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(71) Applicant *(for all designated States except US):* THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* GAMMILL, Ronald, B. [US/US]; 6704 Pleasantview Drive, Kalamazoo, MI 49002 (US). JUDGE, Thomas, M. [US/US]; 411 Wallace, Kalamazoo, MI 49001 (US). MORRIS, Joel [US/US]; 3001 Applelane, Kalamazoo, MI 49008 (US).

(74) Agent: JAMESON, William, G.; Corporate Patents & Trademarks, The Upjohn Company, Kalamazoo, MI 49001 (US).

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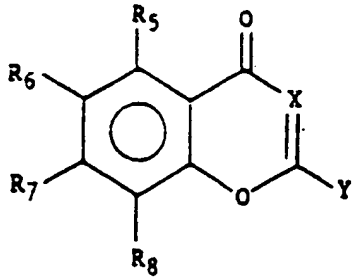

(I)

(57) Abstract

This invention relates to compounds of formula (I) which are useful in association with a pharmaceutical carrier as antiatherosclerotic agents. In addition, various compounds of formula (I) are useful inhibitors of cell proliferation.

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ANTIATHEROSCLEROTIC AND ANTITHROMBOTIC 1-BENZOPYRAN-4-ONES AND 2-AMINO-1,3-BENZOXAZINE-4-ONES

BACKGROUND OF THE INVENTION

The present specification provides methods for use of pharmacologically active substances. Further the present specification provides novel compositions of matter and novel methods of their preparation.

Atherosclerosis in mammals is a disease characterized by the deposition of atherosclerotic plaque on arterial walls. While atherosclerosis exhibits many varied forms and consequences, typical consequences of atherosclerotic diseases include angina pectoris, myocardial infarction, stroke and transient cerebral ischemic attacks. Other forms of atherosclerotic diseases include certain peripheral vascular diseases and other ischemias (e.g., bowel and renal).

Medical science now recognizes that certain forms of atherosclerosis may be preventable or reversible. Agents capable of preventing or reversing atherosclerosis are characterized as exhibiting antiatherosclerotic activity. Since serum lipids have a recognized association with atherogenesis, an important class of antiatherosclerotic agents are those with serum lipid-modifying effects. Serum lipids implicated in atherogenesis include serum cholesterol, serum triglycerides, and serum lipoproteins.

With respect to serum lipoproteins, at least three different classes of these substances have been characterized; high density lipoproteins (HDL's), low density lipoproteins (LDL's), and very low density lipoproteins (VLDL's). HDL's are often referred to as alphalipoproteins, while LDL's and VLDL's are referred to as betalipoproteins. The enhancement of HDL levels (hyperalphalipoproteinemic activity) is postulated to have direct antiatherosclerotic effects. See Eaton, R.P., J. Chron. Dis 31:131-135 (1978). In contrast, agents which reduce serum LDL's and serum VLDL's (hypobetalipoproteinemic agents) are also associated with antiatherogenic effects. See Haust, M.D., "Reaction Patterns of Intimal Mesenchyme to Injury and Repair in Atherosclerosis", Adv. Exp. Med. Biol. 43:35-57 (1974), which postulates that serum LDL is a factor in athero-

sclerotic lesion formation.

Numerous animal models have been developed for assessing antiatherosclerotic activity. Principal among these are models for assessing hypolipoproteinemic activity in the rat and antiatherosclerotic activity in the Japanese quail. For a description of the operation of the hypobetalipoproteinemic rat model, refer to the known methods of Schurr, P.E., et al., "High Volume Screening Procedure for Lypobetalipoproteinemia Activity in Rats", Adv. Exp. Med. Biol. 67: Atherosclerotic Drug Discovery, pp. 215-229, Plenum Press (1975). For a description of the Japanese quail model, see Day, C.E. et al., "Utility of a Selected Line (SEA) of the Japanese Quail (Corturnic Corturnix japonica) for the Discovery of New Anti-Atherosclerosis Drugs", Laboratory Animal Science 27:817-821 (1977).

2-Aminochromones (4H-1-benzopyran-4-ones) are known in the literature. For example, the antiallergic activity of 2-aminochromones has been described in the literature by Mazzei, Balbi, Ermili, Sottofattori and Roma (Mazzei, M., Ballbi, A., Ernili, A., Sottofattori, E., Roma, G., Farmaco. Ed. Sci., (1985) 40, 895 and Mazzei, M., Ermili, A., Balbi, A., Di Braccio, M., Farmaco. Ed. Sci., (1986), 41, 611; CA 106:18313w). The CNS activity of 2-aminochromones has also been described (Balbi, A., Roma, G., Ermili, A., Farmaco. Ed. Sci., (1982) 37, 582; Ermili, A., Mazzei, M., Roma, G., Cacciatore, C., Farmaco. Ed. Sci., (1977), 32, 375 and 713). The nitro derivatives of various 2-aminochromones have recently been described (Balbi, A., Roma, G., Mazzei, M., Ermili, A., Farmaco. Ed. Sci., (1983) 38, 784) and Farmaco. Ed. Sci., 41(7), 548-57. 2-Amino-3-hydroxychromones are described in DE 2205913 and GB 1389186.

U.S. Patent 4,092,416 (see also DE 2555290 and CA 87:102383r) discloses various benzopyrone derivatives exhibiting anti-allergic activity, including 2-{2-[4-(2-methoxyphenyl)-piperazinyl-1]-ethyl}-5-methoxy-4-oxo-4H-1-benzopyran and 2-{2-[4-(2-methoxyphenyl)-piperazinyl-1]-ethyl}-5-(2-hydroxypropoxy)-4-oxo-4H-1-benzopyran.

JA-025657 and JP-259603 describe various 2-amino-3-

carboxamide derivatives and 3-phenyl(optionally substituted)-2-aminochromone derivatives as useful as oncostatic and immunosuppressive agents.

The pharmacomodulation of α-adrenergic blocking agents by a series of benzopyrans, including 2-(1-piperidinylmethylene)-4H-1-benzopyran-4-one, is described in Eur. J. Med. Chem., 1987, 22(6), 539-44; CA 109:92718k.

Structurally, the closest compounds in the literature to 2-(4-morpholinyl)-4H-1-benzopyran-4-one (Cpd 2) is believed to be the 3-hydroxy, 3-methoxy and 3-acetyloxy analogues (i.e., 2-(4-morpholinyl)-3-hydroxychromone, 2-(4-morpholinyl)-3-methoxychromone and 3-(acetyloxy)-2-(4-morpholinyl)chromone) reported by Eiden and Docher (Eiden, F., Dolcher, D., Arch. Pharm. (Weinheim Ger.) (1975) 308, 385) and DE 2205913; CA 83(11):96942w and CA79(19):115440s. 6,7-dimethoxy-2-(4-morpholinyl)chromone is disclosed in J. Chem. Soc., Perkins Trans. 1, (2), 173-4; CA78(9);58275v. 3-Acetyl-2-(4-morpholinyl)chromone is disclosed in Arch. Pharm. 316(1), 34-42; CA98(15):12915g. 3-hydroxy-2-[4-(2-hydroxyethyl)-1-piperazinyl]-4H-1-benzopyran-4-one and 3-hydroxy-2-(4-methyl-1-piperazinyl)-4H-1-benzopyran-4-one are disclosed in Arch. Pharm 308(5), 385-8; CA83(11):96942w. 5,8-dimethoxy-2-(4-methyl-1-piperazinyl)-4H-1-benzopyran-4-one is disclosed in J. Heterocycl. Chem., 18(4), 679-84; CA95(17):150348v.

The synthesis of 2-aminochromones from the corresponding 2-sulphonyl and 2-sulphinyl analogues has been reported by Bantick and Suschitzky (Bantick, J.R., Suschitzky, J.L., J. Heterocyclic Chem., (1981) 18, 679). Also described in this report is the preparation of the HCL and H_2SO_4 salts of several 2-aminochromones.

The anti-platelet activity of some 2-(dialkylamino)chromones, namely: 2-(diethylamino)-5,6-dimethyl-4H-1-benzopyran-4-one,2-(diethylamino)-6,7-dimethyl-4H-1-benzopyran-4-one,2-(diethylamino)-7-hydroxy-5-methyl-4H-1-benzopyran-4-one, 2-(diethylamino)-5-hydroxy-7-methyl-4H-1-benzopyran-4-one, 2-(diethylamino)-6-chloro-8-isopropyl-4H-1-benzopyran-4-one, 2-(diethylamino)-5,7-methoxy-4H-1-benzopyran-4-one, 2-(ethylamino)-5-hydroxy-4H-1-benzopyran-4-one, 2-

(ethylamino)-7-hydroxy-4H-1-benzopyran-4-one, 2-(diethylamino)-7-hydroxy-6-nitro-4H-1-benzopyran-4-one, 2-(diethylamino)-4H-1-benzopyran-4-one,2-(dimethylamino)-7-methoxy-4H-1-benzopyran-4-one, 2-(diethylamino)-7-methoxy-4H-1-benzopyran-4-one, 2-(1-pyrrolidinyl)-7-methoxy-4H-1-benzopyran-4-one, 2-(1-piperidinyl)-7-methoxy-4H-1-benzopyran-4-one, 2-(diethylamino)-7-hydroxy-4H-1-benzopyran-4-one, 2-(1-piperdinyl)-7-hydroxy-4H-1-benzopyran-4-one,2-(ethylamino)-7-methoxy-4H-1-benzopyran-4-one, 2-(diethylamino)-5-hydroxy-4H-1-benzopyran-4-one, 2-(diethylamino)-5-methyl-8-isopropyl-4H-1-benzopyran-4-one, and 2-(diethylamino)-3-(4-morpohoinomethyl)-7-methoxy-4H-1-benzopyran-4-one, was reported by Mazzei et al. in Eur. J. Med. Chem. 23, 237-242 (May-June 1988); CA 110:75246h.

The literature on the use of an ynamine in the synthesis of a 2-aminochromones has been reported by Tronchet, Bachler and Bonenfant (Tronchet, J.M. J., Bachler, B., Bonenfant, A., Helv. Chim. Acta. (1976), 59, 941). In this report, a 2-amino-3-glycosylchromone was prepared.

2-Amino-1,3-benzoxazin-4-ones are also known in the literature. Specifically, 2-morpholinyl-4H-1,3-benzoxazin-4-one and 8-methyl-2-(4-morpholinyl)-4H-1,3-benzoxazin-4-one are described in Netherlands patent application 6,412,966 (see also U.S. 3,491,092), and in the literature (Grigat, E., Putter, R., Schneider, K., Wedemeyer, K., Chem. Ber., (1964) 97, 3036).

The fungicide and analgesic activity of 2-amino-1,3-benzoxazin-4-ones are also claimed by Sankyo in Japn. Tokkyo Koho 79 20,504 (CA 91:157755b) and in Japan (Kokai 72, 17,781 (CA 77:140107e). These patents appear to cover 2-(4-morpholinyl)-4H-1,3-benzoxazin-4-one and 6,7-substituted-2-(4-morpholinyl) analogues for the above indications.

The synthesis of 2-dialkylamino-1,3-benzoxazin-4-ones has been described by Kokel et al (see Tet. Letters (1984) 3837).

2-N-Alkyl and 2-N-aryl-1,3-benzoxazin-4-ones have been described by Palazzo and Giannola (Palazzo, S., Giannola, L.I., Atti. Accad. Sci. Lett. Arti Palermo, Parte 1, (1976) 34(2), 83-7).

2-Benzamidino-1,3-benzoxazin-4-one have been described by

Brunetti, H., and Luthi, C.E. (in Helv. Chim. Acta., (1972) 55, 1566).

PCT/US89/05526, filed 15 December 1989 (published 28 June 1990) discloses various 1-benzopyran-4-ones and 2-amino-1,3-benzoxazines-4-ones, including 2-(4-morpholinyl)-4H-1-benzopyran-4-one, 8-Methyl-2-(4-morpholinyl)-(7-phenylmethoxy)-4H-benzopyran-4-one, 7-[(1-cyclohexyl-1H-tetrazol-5-yl)methoxy]-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one, 8-Methyl-2-(4-morpholinyl)-7-(2-(1-piperidinyl)ethyl)oxy-4H-1-benzopyran-4-one, 8-Methyl-2-(4-morpholinyl)-7-(2-(1-pyrrolidinyl)ethyl)oxy-4H-1-benzopyran-4-one, 7-[2-(ethylphenylamino)ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, as well as their antiatherosclerotic, antithrombotic activity, cell proliferation (inhibitive) and/or inhibitive of platelet aggregation.

BRIEF DESCRIPTION OF THE INVENTION

This invention relates to compounds of the Formula I which are useful in association with a pharmaceutical carrier as antiatherosclerotic agents. In addition, various compounds of the Formula I are useful inhibitors of cell proliferation and/or platelet aggregation.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are represented by Formula I wherein

X is N, or CZ where Z is H, C_1-C_5 alkyl, amino ($-NH_2$) or a halogen atom;

when X is CZ, Y is selected from the group consisting of $-(CH_2)_nNR_9R_{10}$ wherein R_9 and R_{10}, being the same or different, are selected from the group consisting of

(a) hydrogen, with the provisio that R_9 and R_{10} are not both hydrogen;

(b) C_1-C_{12} alkyl;

(c) phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4 alkyl);

(d) $-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)],

(e) $-(CH_2)_n$pyridinyl or

(f) wherein R_9 and R_{10}, taken together with N, form a saturated or unsaturated heterocyclic amine ring selected from the group consisting of

(aa) 4-morpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(bb) 4-thiomorpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(cc) 3-amino-1-pyrrolidine,

(dd) 1-pyrrolidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, $-CH_2OH$, or trifluoromethyl,

(ee) 1-piperidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-(CH_2)_qOH$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$ or phenyl (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl),

(ff) 1-piperazine, 4-(C_1-C_4alkyl)-1-piperazine (preferably 4-methyl-1-piperazine), 4-(cycloC_3-C_6alkyl)-1-piperazine, 4-phenyl-1-piperazine (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl) or 4-pyridinyl-1-piperazine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl, $-CH_2OH$, $-CO_2H$, $-CO_2CH_3$ or $-CO_2CH_2CH_3$

(gg) thiazolidine, thiazolidine-4-carboxylic acid, pipecolinic acid, p-piperazinacetophenone, 1-homopiperazine, 1-methylhomopiperazine, 4-phenyl-1,2-3,6-tetrahydropyridine, proline, tetrahydrofurylamine, 1-(3-hydroxy)pyrrolidine, nipecotamide, 1,2,3,4-tetrahydroisoquinoline or imidazole;

and R_5, R_6, R_7 and R_8, being the same or different, are selected from the group consisting of hydrogen, C_1-C_8 alkyl, $-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl

or $-CO_2(C_1-C_4alkyl)]$, $-(CH_2)_n$naphthyl, $-(CH_2)_n$pyridinyl, $-(CH_2)_qNR_9R_{10}$, -CH=CH-phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)]$, $-CH_2-CH=CH_2$, $-CH=CH-CH_3$, $-CH=CH_2$, $-O-CH_2-CH=CH_2$, -C≡C-phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)]$, $-O-(CH_2)_p$(N-methylpiperdin-3-yl), $-O-(CH_2)_pNR_9R_{10}$ [preferably $-O-(CH_2)_p-4-(C_1-C_4alkyl)$-1-piperazine, $-O-(CH_2)_p$(1-piperidinyl), $-O-(CH_2)_p$(1-pyrrolidinyl), more preferably $-O-(CH_2)_2$-4-methyl-1-piperazine], $-O-CH_2CH(OCH_3)_2$, $-O-(CH_2)_pOR_{15}$ {wherein R_{15} is selected from H, C_1-C_5 alkyl, $-(CH_2)_n$phenyl [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)]$, $-(CH_2)_n$pyridin-1-yl, $-(CH_2)_n$pyridin-2-yl, $-(CH_2)_n$pyridin-3-yl, $-(CH_2)_n$pyridin-4-yl, $-(CH_2)_n-1-(C_1-C_4alkyl)$-1H-5-tetrazole, $-(CH_2)_n$-pyrimidine, $-(CH_2)_n$-2-benzoxazole, $-(CH_2)_n$-2-benzothiazole, $-(CH_2)_n-(C_1-C_4alkyl)$-triazole, $-(CH_2)_n-(C_1-C_4alkyl)$-imidazole}, $-O-(CH_2)_p-O-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S-R_{15}$, $-O-(CH_2)_p-O-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O)-R_{15}$, $-O-(CH_2)_p-S(O_2)-R_{15}$, $-O-(CH_2)_p-S(O)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-[4-[(CH_2)_pOR_{15}]$-1-piperazine], $-O-(CH_2)_p-[4-(CH)(phenyl)_2$-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)]$, $-O-(CH_2)_p-[4-(CH_2)_q$phenyl-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)]$, $-O-(CH_2)_p-[4-(CH_2)_q$pyridinyl-1-piperazine] [pyridinyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl, NR_9R_{10} or $-CO_2(C_1-C_4alkyl)]$, $O-(CH_2)_p-[4-(NR_9R_{10}$ substituted pyridinyl)-1-piperazine, $-O-(CH_2)_p-$(OH substituted 1-piperidine), $-O-(CH_2)_p$-1-pyrrolidin-2-one, $-(CH_2)_nC(O)-(CH_2)_nR_9$, $-(CH_2)_nC(O)O-(CH_2)_pR_9$, $-(CH)_nC(O)O-(CH_2)_pNR_9R_{10}$, $-(CH_2)_nC(O)(CH_2)_nNR_9R_{10}$, NO_2, $-O-(CH_2)_nC(O)-(CH_2)_pR_9$, $-O-(CH_2)_nC(O)O-(CH_2)_pR_9$, $-O-(CH_2)_nC(O)-(CH_2)_nNR_9R_{10}$, $-NR_9R_{10}$, $-N(R_9)(CH_2)_nC(O)-(CH_2)_nR_{10}$, $-N(R_9)-(CH_2)_nC(O)O-(CH_2)_nR_{10}$, $N(R_9)(CH_2)_nC(O)-(CH_2)_nNR_9R_{10}$, $-O-(CH_2)_n$phenyl [wherein phenyl is

optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], -O-$(CH_2)_n$pyridine, $-O(CH_2)_nC(O)$-$(CH_2)_n$pyridine, -O-$(CH_2)_nC(O)O$-$(CH_2)_n$pyridine, $-O(CH_2)_nC(O)$-$N(R_9)(CH_2)_n$pyridine, -O-$(CH_2)_n$quinoxalinyl, -O-$(CH_2)_n$quinolinyl, -O-$(CH_2)_n$pyrazinyl, -O-$(CH_2)_n$naphthyl, -O-$(CH_2)_nC(O)$-$(CH_2)_n$naphthyl, -O-$(CH_2)_nC(O)O$-$(CH_2)_n$naphthyl, -O-$(CH_2)_nC(O)NR_9$-$(CH_2)_n$naphthyl, halo (fluoro, chloro, bromo, iodo), OH, $-(CH_2)_q$-OH, $(CH_2)_qOC(O)R_9$, $-(CH_2)_qOC$-(O)-NR_9R_{10}, -(1-cyclohexyl-1H-tetrazol-5-yl)C_1-C_4 alkoxy, -[1-(C_1-C_5alkyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy (including -(1-cycloC_3-C_5 alkyl-1H-tetrazol-5-yl)C_1C_4alkoxy), -[1-(phenyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], -[1-(pyridinyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, -[1-(1-phenylethyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, -C_1-C_4 alkoxyl, or a group of Formula II (see Formula Sheet) wherein R′ is methyl or carboxy, R′′ is hydrogen and R′′′ is selected from benzyl [optionally substituted with one, two or three groups selected from hydroxy, halogen or phenoxy (optionally substituted with one, two or three groups selected from hydroxy or halogen)], C_1-C_5 alkyl, $-(CH_2)_nCO_2H$, $-CH_2SH$, $-CH_2SCH_3$, imidazolinylmethylene, indolinylmethylene, $CH_3CH(OH)$, CH_2OH, $H_2N(CH_2)_4$-(optionally in protected form) or $H_2NC(NH)NH(CH_2)_3$ (optionally in protected form); with the overall proviso that at least one member of R_5, R_6, R_7 or R_8 is selected from the group consisting of $-CH=CH_2$, -O-$(CH_2)_p$OH, -O-$(CH_2)_p$-O-$(CH_2)_n$pyridin-2-yl, -O-$(CH_2)_p$-O-$(CH_2)_n$pyridin-3-yl, -O-$(CH_2)_p$-O-$(CH_2)_n$pyridin-4-yl, -O-$(CH_2)_p$-O-$(CH_2)_n$-1-(C_1-C_4alkyl)-1H-5-tetrazole, -O-$(CH_2)_p$-O-$(CH_2)_n$-pyrimidine, -O-$(CH_2)_p$-O-$(CH_2)_n$-2-benzoxazole, -O-$(CH_2)_p$-O-$(CH_2)_n$-2-benzothiazole, -O-$(CH_2)_p$-O-$(CH_2)_n$-(C_1-C_4alkyl)-triazole, -O-$(CH_2)_p$-O-$(CH_2)_n$-(C_1-C_4alkyl)-imidazole, -O-$(CH_2)_p$-O-$(CH_2)_p$-OR_{15}, -O-$(CH_2)_p$-S-R_{15}, -O-$(CH_2)_p$-O-$(CH_2)_pNR_9R_{10}$, -O-$(CH_2)_p$-S-$(CH_2)_pNR_9R_{10}$, -O-$(CH_2)_p$-S-$(CH_2)_p$-OR_{15}, -O-$(CH_2)_p$-S(O)-R_{15}, -O-$(CH_2)_p$-$S(O_2)$-R_{15}, -O-$(CH_2)_p$-S(O)-$(CH_2)_pNR_9R_{10}$, -O-$(CH_2)_p$-S(O)-$(CH_2)_p$-OR_{15}, -O-$(CH_2)_p$-$S(O_2)$-$(CH_2)_pNR_9R_{10}$, -O-$(CH_2)_p$-$S(O_2)$-$(CH_2)_p$-OR_{15}, -O-$(CH_2)_p$-[4-[$(CH_2)_pOR_{15}$]-1-piperazine], -O-$(CH_2)_p$-[4-(CH)$(phenyl)_2$-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-

C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-O-(CH_2)_p-[4-(CH_2)_q$phenyl-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-O-(CH_2)_p-[4-(CH_2)_q$pyridinyl-1-piperazine] [pyridinyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl, NR_9R_{10} or $-CO_2(C_1$-C_4alkyl)], $O-(CH_2)_p-[4-(NR_9R_{10}$ substituted pyridinyl)-1-piperazine, $-O-(CH_2)_p-$(OH substituted 1-piperidine), $-O-(CH_2)_p-$1-pyrrolidin-2-one;

when X is N, Y is selected from the group consisting of $-NR_9R_{10}$ wherein R_9 and R_{10}, being the same or different, are selected from the group consisting of

(a) hydrogen, with the provisio that R_9 and R_{10} are not both hydrogen;

(b) C_1-C_{12} alkyl;

(c) phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl);

(d) $-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)],

(e) $-(CH_2)_n$pyridinyl or (f) wherein R_9 and R_{10}, taken together with N, form a saturated or unsaturated heterocyclic amine ring selected from the group consisting of

(aa) 4-morpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(bb) 4-thiomorpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(cc) 3-amino-1-pyrrolidine,

(dd) 1-pyrrolidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, $-CH_2OH$, or trifluoromethyl,

(ee) 1-piperidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-(CH_2)_qOH$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$ or phenyl (wherein phenyl is optionally

substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl),

(ff) 1-piperazine, 4-(C_1-C_4alkyl)-1-piperazine (preferably 4-methyl-1-piperazine), 4-phenyl-1-piperazine (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl) or 4-pyridinyl-1-piperazine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl, $-CH_2OH$, $-CO_2H$, $-CO_2CH_3$ or $-CO_2CH_2CH_3$, and

(gg) thiazolidine, thiazolidine-4-carboxylic acid, pipecolinic acid, p-piperazinacetophenone, 1-homopiperazine, 1-methylhomopiperazine, 4-phenyl-1,2-3,6-tetrahydropyridine, proline, tetrahydrofurylamine, 1-(3-hydroxy)pyrrolidine, nipecotamide, 1,2,3,4-tetrahydroisoquinoline or imidazole;

and R_5, R_6, R_7 and R_8, being the same or different, are selected from the group consisting of hydrogen, C_1-C_8 alkyl, $-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-(CH_2)_n$naphthyl, $-(CH_2)_n$pyridinyl, $-(CH_2)_qNR_9R_{10}$, -CH=CH-phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-CH_2-CH=CH_2$, $-CH=CH-CH_3$, $-CH=CH_2$, $-O-CH_2-CH=CH_2$, -C≡C-phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-O(CH_2)_p$(N-methylpiperdin-3-yl), $-O-(CH_2)_pNR_9R_{10}$, $-O-CH_2CH(OCH_3)_2$, $-O-(CH_2)_pOR_{15}$ {wherein R_{15} is selected from H, C_1-C_5 alkyl, $-(CH_2)_n$phenyl [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-(CH_2)_n$pyridin-1-yl, $-(CH_2)_n$pyridin-2-yl, $-(CH_2)_n$pyridin-3-yl, $-(CH_2)_n$pyridin-4-yl, $-(CH_2)_n$-1-(C_1-C_4alkyl)-1H-5-tetrazole, $-(CH_2)_n$-pyrimidine, $-(CH_2)_n$-2-benzoxazole, $-(CH_2)_n$-2-benzothiazole, $-(CH_2)_n$-(C_1-C_4alkyl)-triazole, $-(CH_2)_n$-(C_1-C_4alkyl)-imidazole}, $-O-(CH_2)_p-O-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S-R_{15}$, $-O-(CH_2)_p-O-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O)-R_{15}$, -O-

$(CH_2)_p$-$S(O_2)$-R_{15}, -O-$(CH_2)_p$-S(O)-$(CH_2)_p$$NR_9R_{10}$, -O-$(CH_2)_p$-S(O)-$(CH_2)_p$-$OR_{15}$, -O-$(CH_2)_p$-$S(O_2)$-$(CH_2)_p$$NR_9R_{10}$, -O-$(CH_2)_p$-$S(O_2)$-$(CH_2)_p$-$OR_{15}$, -O-$(CH_2)_p$-[4-[$(CH_2)_p$$OR_{15}$]-1-piperazine], -O-$(CH_2)_p$-[4-(CH)(phenyl)$_2$-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or -CO_2(C_1-C_4alkyl)], -O-$(CH_2)_p$-[4-$(CH_2)_q$phenyl-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or -CO_2(C_1-C_4alkyl)], -O-$(CH_2)_p$-[4-$(CH_2)_q$pyridinyl-1-piperazine] [pyridinyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl, NR_9R_{10} or -CO_2(C_1-C_4alkyl)], O-$(CH_2)_p$-[4-(NR_9R_{10} substituted pyridinyl)-1-piperazine, -O-$(CH_2)_p$-(OH substituted 1-piperidine), -O-$(CH_2)_p$-1-pyrrolidin-2-one, -$(CH_2)_n$C(O)-$(CH_2)_n$$R_9$, -$(CH_2)_n$C(O)O-$(CH_2)_p$$R_9$, -$(CH)_n$C(O)O-$(CH_2)_p$$NR_9R_{10}$, -$(CH_2)_n$C(O)$(CH_2)_n$$NR_9R_{10}$, NO_2, -O-$(CH_2)_n$C(O)-$(CH_2)_p$$R_9$, -O-$(CH_2)_n$C(O)O-$(CH_2)_p$$R_9$, -O-$(CH_2)_n$C(O)-$(CH_2)_n$$NR_9R_{10}$, -$NR_9R_{10}$, -N($R_9$)$(CH_2)_n$C(O)-$(CH_2)_n$$R_{10}$, -N($R_9$)-$(CH_2)_n$C(O)O-$(CH_2)_n$$R_{10}$, N($R_9$)$(CH_2)_n$C(O)-$(CH_2)_n$$NR_9R_{10}$, -O-$(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or -CO_2(C_1-C_4alkyl), -O-$(CH_2)_n$pyridine, -O$(CH_2)_n$C(O)-$(CH_2)_n$pyridine, -O-$(CH_2)_n$C(O)O-$(CH_2)_n$pyridine, -O$(CH_2)_n$C(O)-N(R_9)$(CH_2)_n$pyridine, -O-$(CH_2)_n$quinoxalinyl, -O-$(CH_2)_n$quinolinyl, -O-$(CH_2)_n$pyrazinyl, -O-$(CH_2)_n$naphthyl, -O-$(CH_2)_n$C(O)-$(CH_2)_n$naphthyl, -O-$(CH_2)_n$C(O)O-$(CH_2)_n$naphthyl, -O-$(CH_2)_n$C(O)NR_9-$(CH_2)_n$naphthyl, halo (fluoro, chloro, bromo, iodo), OH, -$(CH_2)_q$-OH, $(CH_2)_q$OC(O)R_9, -$(CH_2)_q$OC-(O)-NR_9R_{10}, -(1-cyclohexyl-1H-tetrazol-5-yl)C_1-C_4 alkoxy, -[1-(C_1-C_5alkyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy (including -(1-cycloC_3-C_5alkyl-1H-tetrazol-5-yl)C_1-C_4 alkoxy), -[1-(phenyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or -CO_2(C_1-C_4alkyl)], -[1-(pyridinyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, -[1-(1-phenylethyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, or -C_1-C_4 alkoxyl, or a group of Formula II (see Formula Sheet) wherein R′ is methyl or carboxy, R′′ is hydrogen and R′′′ is selected from benzyl [optionally substituted with one, two or three groups selected from hydroxy, halogen or phenoxy (optionally substituted with one,

two or three groups selected from hydroxy or halogen)], C_1-C_5 alkyl, $-(CH_2)_nCO_2H$, $-CH_2SH$, $-CH_2SCH_3$, imidazolinylmethylene, indolinylmethylene, $CH_3CH(OH)$, CH_2OH, $H_2N(CH_2)_4$-(optionally in protected form) or $H_2NC(NH)NH(CH_2)_3$ (optionally in protected form) with the overall proviso that at least one member of R_5, R_6, R_7 or R_8 is selected from the group consisting of $-CH=CH_2$, $-O-(CH_2)_pOH$, $-O-(CH_2)_p-O-(CH_2)_n$pyridin-2-yl, $-O-(CH_2)_p-O-(CH_2)_n$pyridin-3-yl, $-O-(CH_2)_p-O-(CH_2)_n$pyridin-4-yl, $-O-(CH_2)_p-O-(CH_2)_n$-1-(C_1-C_4alkyl)-1H-5-tetrazole, $-O-(CH_2)_p-O-(CH_2)_n$-pyrimidine, $-O-(CH_2)_p-O-(CH_2)_n$-2-benzoxazole, $-O-(CH_2)_p-O-(CH_2)_n$-2-benzothiazole, $-O-(CH_2)_p-O-(CH_2)_n-(C_1-C_4alkyl)$-triazole, $-O-(CH_2)_p-O-(CH_2)_n-(C_1-C_4alkyl)$-imidazole, $-O-(CH_2)_p-O-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S-R_{15}$, $-O-(CH_2)_p-O-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O)-R_{15}$, $-O-(CH_2)_p-S(O_2)-R_{15}$, $-O-(CH_2)_p-S(O)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-[4-[(CH_2)_pOR_{15}]$-1-piperazine], $-O-(CH_2)_p-[4-(CH)(phenyl)_2$-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)$], $-O-(CH_2)_p-[4-(CH_2)_q$phenyl-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)$], $-O-(CH_2)_p-[4-(CH_2)_q$pyridinyl-1-piperazine] [pyridinyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl, NR_9R_{10} or $-CO_2(C_1-C_4alkyl)$], $O-(CH_2)_p-[4-(NR_9R_{10}$ substituted pyridinyl)-1-piperazine, $-O-(CH_2)_p-$(OH substituted 1-piperidine), $-O-(CH_2)_p$-1-pyrrolidin-2-one;

n is 0-5, preferably 0 or one;

p is 2-5, preferably 2 or 3;

q is 1-5, preferably 1 or 2;

and pharmaceutically acceptable salts thereof.

X is preferably CZ where Z is H or C_1-C_5 alkyl, more preferably H or methyl, most preferably H.

When X is CZ, Y is preferably selected from the group consiting of $-(CH_2)_nNR_9R_{10}$ wherein R_9 and R_{10}, taken together with N, form a saturated or unsaturated heterocyclic amine ring selected from the group consisting of:

(aa) 4-morpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(bb) 4-thiomorpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(cc) 3-amino-1-pyrrolidine,

(dd) 1-pyrrolidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, $-CH_2OH$, or trifluoromethyl,

(ee) 1-piperidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-(CH_2)_qOH$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$ or phenyl (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl), and

(ff) 1-piperazine, 4-methyl-1-piperazine, 4-phenyl-1-piperazine (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl) or 4-pyridinyl-1-piperazine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-CH_2OH$, $-CO_2H$, $-CO_2CH_3$ or $-CO_2CH_2CH_3$.

When X is CZ wherein Z is H or C_1-C_5 alkyl (most preferably H), Y is more preferably selected from the group consisting of $-(CH_2)_nNR_9R_{10}$ wherein n is 0 or 1 (most preferably 0) and R_9 and R_{10}, taken together with N, form:

(aa) morpholine (preferably 4-morpholine) optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl or phenyl (wherein phenyl is optionally substituted with one or 2 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl);

and preferably, at least one member selected from R_5, R_6, R_7 or R_8 is selected from the group consisting of $-O-(CH_2)_p-S-R_{15}$, $-O-(CH_2)_p-[4-(CH)phenyl)_2-1-piperazine]$, $-CH=CH_2$, or $-O-(CH_2)_pO-(CH_2)_pOR_{15}$; more preferably,

(i) R_5, R_6, and R_7 are each hydrogen, and R_8 is selected from: $-O-(CH_2)_p-[4-(CH)phenyl)_2-1-piperazine]$, or $-O-(CH_2)_p-S-$

R_{15}; or

(ii) R_5 and R_6 are hydrogen, R_8 is hydrogen, halo, $-CH=CH_2$, or C_1-C_5 alkyl, and R_7 is selected from: $-O-(CH_2)_p-[4-(CH)phenyl)_2-1-piperazine]$, or $-O-(CH_2)_p-S-R_{15}$.

X is most preferably CH.

Y is most preferably 4-morpholinyl.

R_8 is preferably hydrogen or C_1-C_5 alkyl, more preferably hydrogen or methyl.

R_{15} is preferably hydrogen, C_1-C_5 alkyl, $-(CH_2)_n$phenyl, $-(CH_2)_n$pyridin-2-yl or $-(CH_2)_n$pyridin-3-yl.

Examples of preferred compounds include: Compounds 208, 233, 266, 283, 293, 304, 326, and 347; as well as salts thereof.

Accordingly the present invention includes the novel 2-amino(4H)-1-benzopyran-4-ones and 2-aminoalkyl(4H)-1-benzopyran-4-ones of Formula I when X is CZ and the antiatherosclerotic utility of said compounds as well as the antiatherosclerotic utility of the known compounds of Formula I, including the 2-amino-1,3-benzoxazine-4-ones of Formula IB.

The carbon content of various hydrocarbon containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_i-C_j indicates a carbon atoms content of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, C_1-C_3 alkyl refers to alkyl of 1-3 carbon atoms, inclucive, or methyl, ethyl, propyl, and isopropyl.

With respect to the above, C_1-C_4 alkyl is methyl, ethyl, propyl, or butyl, including isomeric forms thereof. Similarly, C_1-C_6 alkyl is methyl, ethyl, propyl, butyl, pentyl, hexyl, and isomeric forms thereof.

The term "halo" includes fluoro, chloro, bromo and iodo.

All temperatures throughout the specification are expressed in degrees Celcius (°C).

Examples of C_1-C_8 alkylthiomethyl are methylthiomethyl, ethylthiomethyl, propylthiomethyl, butylthiomethyl, pentylthiomethyl, hexylthiomethyl, and heptylthiomethyl, and isomeric forms thereof.

Examples of C_1-C_8 alkoxymethyl are methoxymethyl,

ethoxymethyl, propoxymethyl, butoxymethyl, pentoxymethyl, butoxymethyl, pentoxymethyl, hexoxymethyl, and heptoxymethyl, and isomeric forms thereof.

Examples of heterocylic amines corresponding to heterocyclic amine rings according to $-NR_9N_{10}$ are:

4-morpholine,
4-phenyl-1-piperazine,
4-(2-pyridinyl)-1-piperazine,
2,6-dimethyl-4-morpholine,
1-pyrrolidine,
4-methyl-1-piperazine,
1-piperidine,
4-phenyl-1-piperidine
thiazolidine,
3-piperidine methanol,
2-piperidine methanol,
pipecolic acid,
3-piperidine ethanol,
2-piperidine ethanol,
1-piperazine propanol,
p-piperazinoacetophenone,
4-phenyl-1,2,3,6-tetrahydropyridine,
4-phenylpiperidine,
proline,
1-(3-hydroxy)pyrrolidine,
tetrahydrofurylamine,
pyrrolidimethanol,
3-pyrroline,
thiazolidine-4-carboxylic acid,
thiomorpholine,
nipecotamide,
2-methylpiperidine,
3-methylpiperidine,
4-methylpiperidine,
N-methylpiperazine,
1-methylhomopiperazine,
1-acetylpiperazine,
N-carboethoxypiperazine,

3-methylpiperazine-2-carboxylic acid,
2-methylpiperazine,
2,3,5,6,-tetramethylpiperazine,
1,4-dimethylpiperazine,
2,6-dimethylpiperazine,
2-methyl-1-phenylpiperazine,
1-(1-phenylethyl)piperazine,
1-(2-pyrazinyl)piperazine,
1-cyclopropylpiperazine,
1-cyclobutylpiperazine,
1,2,3,4-tetrahydroisoquinoline,
imidazole,
homopiperdine, and pharmaceutically acceptable salts and hydrates thereof.

Examples of $-O(CH_2)_p$(N-methylpiperdin-3-yl) include (2-(N-methylpiperdin-3-yl)ethyl)oxy, (3-(N-methylpiperdin-3-yl)propyl)oxy, (4-(N-methylpiperdin-3-yl)butyl)oxy.

Examples of $-O-(CH_2)_pNR_9R_{10}$ include (2-(1-piperidinyl)ethyl)oxy, (2-(4-morpholinyl)ethyl)oxy, (2-(1-pyrrolidinyl)ethyl)oxy, (3-(N-methylpiperazinyl)propyl)oxy, (4-(N-ethyl-N-phenylamino)butyl)oxy, (5-(diethylamino)pentyl)oxy, (2-(4-benzylpiperazinyl)ethyl)oxy, and (3-(N,N-diisopropyl)propyl)oxy.

Examples of $O-(CH_2)_pOR_{15}$ include (2-methoxyethyl)oxy, (3-butoxypropyl)oxy, (4-phenoxybutyl)oxy, (2-benzyloxyethyl)oxy, (2-(2-(1-piperidinyl)ethoxy)ethyl)oxy and (3-(3-picolylmethoxy)propyl)oxy.

Examples of $-(CH_2)_n$pyridinyl include 2-pyridyl, 3-pyridylmethyl and 4-pyridylethyl.

Examples of $-(CH_2)_n$piperdinyl include 1-piperidinyl, 1-peiperidinylmethyl, 2-(1-piperidinyl)ethyl and 3-(1-piperidinyl)propyl.

Examples of -(CH2)qNR9R10 include (1-piperidinyl)methyl, 2-(4-morpholinyl)ethyl, 3-(1-pyrrolindinyl)propyl and 4-(1-piperazinyl)butyl.

Examples of $-(CH_2)_nC(O)-(CH_2)_nR_9$ include acetyl, acetylmethyl, methylacetylmethyl, methylacetylethyl, phenylacetyl, phenylacetylmethyl, 2-(phenylacetyl)ethyl, 2-

pyridylacetyl, 3-pyridylacetylmethyl, 3-(t-butylacetyl)propyl and 4-(ethylacetyl)butyl.

Examples of $-(CH_2)_nC(O)O-(CH_2)_pR_9$ include carbomethoxy, carbomethoxymethyl, 2-(carbomethoxy)ethyl, carbophenylmethoxy, carbophenylmethoxymethyl, 2-(carbo(3-pyridyl)methoxy)ethyl, carboethoxymethyl and 3-(carbopropoxy)propoxy.

Examples of $-(CH_2)_nC(O)O-(CH_2)_pNR_9R_{10}$ include $-C(O)O-(CH_2)_2N(ethyl)_2$, $-(CH_2)C(O)O-(CH_2)_2N(CH_3)(phenyl)$, $-(CH_2)_3C(O)O-(CH_2)_3$(1-pyrrolidine), $-(CH_2)_3C(O)O-(CH_2)_2$(1-piperidinyl), and $-(CH_2)C(O)O-(CH_2)_2$(4-morpholinyl).

Examples of $-(CH_2)_nC(O)(CH_2)_nNR_9R_{10}$ include $-(CH_2)C(O)(CH_2)N(ethyl)_2$, $-(CH_2)_2C(O)(CH_2)_2N(methyl)(phenyl)$, $-C(O)$(1-pyrrolidine), $-(CH_2)_2C(O)(CH_2)_3$(1-piperidine), and $-(CH_2)_3C(O)(CH_2)$(4-morpholine).

Examples of $-O-(CH_2)_nC(O)-(CH_2)_pR_9$ include $-O-(CH_2)C(O)-(CH_2)(CH_3)$, $-O-C(O)-(CH_2)_2(CH_3)$, $-O-(CH_2)_3C(O)-(CH_2)$phenyl, $-O-(CH_2)_2C(O)-(CH_2)_3$(2-pyridyl), $-O-(CH_2)C(O)-(CH_2)_2$(3-pyridyl) and $-O-(CH_2)_4C(O)-(CH_2)_4$(t-butyl).

Examples of $-O-(CH_2)_nC(O)O-(CH_2)_pR_9$ include $-O-(CH_2)C(O)O-(CH_2)(CH_3)$, $-O-C(O)O-(CH_2)_2(CH_3)$, $-O-(CH_2)_2C(O)O-(CH_2)_3$(phenyl) and $-O-(CH_2)_3C(O)O-(CH_2)_2$(3-pyridyl).

Examples of $-O-(CH_2)_nC(O)-(CH_2)_nNR_9R_{10}$ include $-O-(CH_2)C-(O)-(CH_2)N(CH_3)_2$, $-O-C(O)-(CH_2)$(1-pyrrolidine), $-O-(CH_2)C(O)-$(1-piperidine), $-O-(CH_2)_2C(O)-(CH_2)$(1-N-methylpiperazine), $-O-(CH_2)_2C(O)-(CH_2)_2$(4-morpholine), $-O-(CH_2)C(O)-(CH_2)_3$(cyclohexylamine), $-O-(CH_2)_2C(O)-(CH_2)_3$(t-butylamine), $-O-(CH_2)C(O)-(CH_2)_2$(1-phenylethylamine), $-O-(CH_2)C(O)-(CH_2)_2$(aniline), $-O-(CH_2)C(O)-(CH_2)$(L-phenylalanine ethyl ester) and $-O-(CH_2)_2nC(O)-(CH_2)_3$(3-pyridylamine).

Examples of $-N(R_9)(CH_2)_nC(O)-(CH_2)_nR_{10}$ include $-N(CH_3)C(O)-(CH_3)$, $-N(H)(CH_2)_2C(O)-(CH_2)$(phenyl), $-N(H)(CH_2)C(O)-(CH_2)_2$(3-pyridyl) and $-N(CH_3)(CH_2)_3C(O)-(CH_2)(CH_3)$.

Examples of $-N(R_9)-(CH_2)_nC(O)O-(CH_2)_nR_{10}$ include $-N(H)-(CH_2)C(O)O-(CH_3)$, $-N(H)-(CH_2)_2C(O)O-(CH_2)$(benzyl), $-N(H)-(CH_2)_2-C(O)O-(CH_2)$(3-pyridyl) and $-N(CH_3)-(CH_2)C(O)O-(CH_2)_2$(t-butyl).

Examples of $-N(R_9)(CH_2)_nC(O)-(CH_2)_nNR_9R_{10}$ include $-N(H)(CH_2)C(O)-(CH_2)N(CH_3)_2$, $-N(H)C(O)-(CH_2)$(1-pyrrolidine), $-N(H)(CH_2)_2C(O)-(CH_2)_2$(1-piperidine), and $-N(CH_3)(CH_2)C(O)-$

$(CH_2)_2$(4-morpholine).

Examples of -O-$(CH_2)_n$phenyl include 2-(4-trifluoromethylphenyl)ethoxy, 4-chlorophenoxy, 4-fluorophenylmethoxy, 3-(4-methoxyphenyl)propoxy, 4-(2-methyl-4-fluorophenyl)butoxy, 2-(2-methoxyphenyl)ethoxy, 3-methoxyphenylmethoxy, 4-carbomethoxyphenylmethoxy, 2-(3,4-dichlorophenyl)ethoxy, 4-ethoxyphenylmethoxy, 3-(4-nitrophenyl)propoxy, 4-t-butylphenylmethoxy, 4-benzyloxyphenylmethoxy and 2-(3-triflouromethylphenyl)ethoxy.

Examples of -O-$(CH_2)_n$pyridine include 2-pyridyloxy, 3-pyridylmethoxy and 2-(4-pyridyl)ethoxy.

Examples of -O$(CH_2)_n$C(O)-$(CH_2)_n$pyridine include -O(CH_2)C(O)-(CH_2)(2-pyridine), -O$(CH_2)_3$C(O)-(CH_2)(3-pyridine) and -O$(CH_2)_2$C(O)-$(CH_2)_3$(4-pyridine).

Examples of -O-$(CH_2)_n$C(O)O-$(CH_2)_n$pyridine include -O(CH_2)C(O)O-(CH_2)(2-pyridine),-O$(CH_2)_3$C(O)O-(CH_2)(3-pyridine) and -O$(CH_2)_2$C(O)O-$(CH_2)_3$(4-pyridine).

Examples of -O$(CH_2)_n$C(O)-N(R_9)$(CH_2)_n$pyridine include -O(CH_2)C(O)-N$(CH_3)(CH_2)$(2-pyridine), -O$(CH_2)_2$C(O)-N$(CH_3)(CH_2)$(3-pyridine) and -O(CH_2)C(O)-N(benzyl)$(CH_2)_2$(4-pyridine).

Examples of -O-$(CH_2)_n$quinoxalinyl include 2-quinoxalinyloxy, 2-quinoxalinylmethoxy and 2-(2-quinoxalinyl)ethoxy.

Examples of -O-$(CH_2)_n$quinolinyl include 2-quinolinyloxy, 2-quinolinylmethoxy and 2-(2-quinolinyl)ethoxy.

Examples of -O-$(CH_2)_n$pyrazinyl include 2-pyrazinyloxy, 2-pyrazinylmethoxy and 2-(2-pyrazinyl)ethoxy.

Examples of -O-$(CH_2)_n$naphthyl include 1-naphthyloxy, 2-naphthylmethoxy and 2-(1-naphthyl)ethoxy.

Examples of -O-$(CH_2)_n$C(O)-$(CH_2)_n$naphthyl include -O-(CH_2)C(O)-(CH_2)(1-naphthyl), -O-$(CH_2)_2$C(O)-(CH_2)(2-naphthyl), -O-C(O)-(CH_2)(1-naphthyl) and -O-(CH_2)2C(O)-$(CH_2)_2$(2-naphthyl).

Examples of -O-$(CH_2)_n$C(O)O-$(CH_2)_n$naphthyl include -O-(CH_2)C(O)O-(CH_2)(1-naphthyl), -O-$(CH_2)_2$C(O)O-(CH_2)(2-naphthyl), -O-C(O)O-(CH_2)(1-naphthyl) and -O-(CH_2)2C(O)O-$(CH_2)_2$(2-naphthyl).

Examples of -O-$(CH_2)_n$C(O)NR_9-$(CH_2)_n$naphthyl include -O-

$(CH_2)C(O)N(H)(CH_2)$(1-naphthyl), $-O-(CH_2)C(O)N(CH_3)(CH_2)_2$(2-naphthyl) and $-O-(CH_2)C(O)N$(benzyl)$(CH_2)_3$(1-naphthyl).

Examples of $-(CH_2)_q-OH$ include hydroxymethyl, hydroxyethyl and hydroxybutyl.

Examples of $(CH_2)_qOC(O)R_9$ include $(CH_2)OC(O)$methyl, $(CH_2)_2OC(O)$ethyl, $(CH_2)_3OC(O)$phenyl, $(CH_2)_4OC(O)$(3-pyridyl) and $(CH_2)OC(O)$thiophene.

Examples of $-(CH_2)_qOC(O)-NR_9R_{10}$ include $-(CH_2)OC(O)-N(CH_2)_2$, $-(CH_2)_2OC(O)-N(ethyl)_2$, $-(CH_2)_3OC(O)-$(1-pyrrolidine), $-(CH_2)_4OC(O)-$(1-piperidine) and $-(CH_2)OC(O)-$N-benzylamine.

Examples of -(1-cyclohexyl-1H-tetrazol-5-yl)C_1-C_4 alkoxy, -[1-(C_1-C_5alkyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy include -(1-cyclohexyl-1H-tetrazol-5-yl)methoxy, -(1-cyclohexyl-1H-tetrazol-5-yl)ethoxy, -[1-(methyl)-1H-tetrazol-5-yl]methoxy, -[1-(cyclopropyl)-1H-tetrazol-5-yl]ethoxy,-[1-(1-tert-butyl)-1H-tetrazol-5-yl]propoxy and -[1-(cyclopentyl)-1H-tetrazol-5-yl]methoxy.

Examples of -[1-(phenyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl) include -[1-(phenyl)-1H-tetrazol-5-yl]methoxy,-[1-(phenyl)-1H-tetrazol-5-yl]ethoxy, -[1-(4-methoxyphenyl)-1H-tetrazol-5-yl]methoxy, -[1-(4-fluorophenyl)-1H-tetrazol-5-yl]propoxy.

Examples of -[1-(pyridinyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy or -[1-(1-phenylethyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy include -[1-(2-pyridinyl)-1H-tetrazol-5-yl]methoxy,-[1-(3-pyridinyl)-1H-tetrazol-5-yl]ethoxy, -[1-(4-pyridinyl)-1H-tetrazol-5-yl]propoxy, -[1-(1-phenylethyl)-1H-tetrazol-5-yl]methoxy, -[1-(1-phenylethyl)-1H-tetrazol-5-yl]ethoxy.

Examples of $-(CH_2)_n-$1-(C_1-C_4alkyl)-1H-5-tetrazole include $-CH_2-$1-methyl-1H-5-tetrazole, 1-methyl-1H-5-tetrazole, and $-(CH_2)_2-$1-methyl-1H-5-tetrazole.

Examples of $-(CH_2)_n-$pyrimidine include $-CH_2-$pyrimidine, $-(CH_2)_2-$pyrimidine, pyrimidine.

Examples of $-(CH_2)_n-$2-benzoxazole include $-(CH_2)-$2-benzoxazole, $-(CH_2)_2-$2-benzoxazole, and 2-benzoxazole.

Examples of $-(CH_2)_n-$2-benzothiazole include $-(CH_2)-$2-benzothiazole, $-(CH_2)_2-$2-benzothiazole, and 2-benzothiazole.

Examples of -$(CH_2)_n$-(C_1-C_4alkyl)-triazole include -(CH_2)-methyl-triazole, -$(CH_2)_2$-methyl-triazole, and -methyl-triazole.

Examples of -$(CH_2)_n$-(C_1-C_4alkyl)-imidazole include -(CH_2)-methyl-imidazole, -$(CH_2)_2$-methyl-imidazole, and -methyl-imidazole.

Examples of -O-$(CH_2)_p$-O-$(CH_2)_p$-OR_{15} include -O-$(CH_2)_2$-O-$(CH_2)_2$-O-benzyl, -O-$(CH_2)_2$-O-$(CH_2)_2$-O-methyl, -O-$(CH_2)_2$-O-$(CH_2)_2$-O-phenyl, and -O-$(CH_2)_2$-O-$(CH_2)_2$-O-pyridinyl.

Examples of -O-$(CH_2)_p$-S-R_{15} include -O-$(CH_2)_2$-S-1-methyl-1H-5-tetatrazole, -O-$(CH_2)_2$-S-pyrimidine, -O-$(CH_2)_2$-S-pyridine, -O-$(CH_2)_2$-S-benzyl.

Examples of -O-$(CH_2)_p$-O-$(CH_2)_p$NR_9R_{10} include -O-$(CH_2)_2$-O-$(CH_2)_2$-1-piperidine, -O-$(CH_2)_2$-O-$(CH_2)_2$-4-methyl-1-piperazine, -O-$(CH_2)_2$-O-$(CH_2)_2$-diethylamine, and -O-$(CH_2)_2$-O-$(CH_2)_2$-4-pyridinyl-1-piperazine.

Examples of -O-$(CH_2)_p$-S-$(CH_2)_p$NR_9R_{10} include -O-$(CH_2)_2$-S-$(CH_2)_2$-1-piperidine, -O-$(CH_2)_2$-S-$(CH_2)_2$-4-methyl-1-piperazine, -O-$(CH_2)_2$-S-$(CH_2)_2$-diethylamine, -O-$(CH_2)_2$-S-$(CH_2)_2$-4-pyridinyl-1-piperazine.

Examples of -O-$(CH_2)_p$-S-$(CH_2)_p$-OR_{15} include -O-$(CH_2)_2$-S-$(CH_2)_2$-O-benzyl, -O-$(CH_2)_2$-S-$(CH_2)_2$-O-methyl, -O-$(CH_2)_2$-S-$(CH_2)_2$-O-phenyl, -O-$(CH_2)_2$-S-$(CH_2)_2$-O-pyridinyl.

Examples of -O-$(CH_2)_p$-S(O)-R_{15} include -O-$(CH_2)_2$-S(O)-1-methyl-1H-5-tetatrazole, -O-$(CH_2)_2$-S(O)-pyrimidine, -O-$(CH_2)_2$-S(O)-pyridine, and -O-$(CH_2)_2$-S(O)-benzyl.

Examples of -O-$(CH_2)_p$-S(O_2)-R_{15} include -O-$(CH_2)_2$-S(O_2)-1-methyl-1H-5-tetatrazole, -O-$(CH_2)_2$-S(O_2)-pyrimidine, -O-$(CH_2)_2$-S(O_2)-pyridine, and -O-$(CH_2)_2$-S(O_2)-benzyl.

Examples of -O-$(CH_2)_p$-S(O)-$(CH_2)_p$NR_9R_{10} include -O-$(CH_2)_2$-S(O)-$(CH_2)_2$-1-piperidine, -O-$(CH_2)_2$-S(O)-$(CH_2)_2$-4-methyl-1-piperazine, -O-$(CH_2)_2$-S(O)-$(CH_2)_2$-diethylamine, and -O-$(CH_2)_2$-S(O)-$(CH_2)_2$-4-pyridinyl-1-piperazine.

Examples of -O-$(CH_2)_p$-S(O)-$(CH_2)_p$-OR_{15} include -O-$(CH_2)_2$-S(O)-$(CH_2)_2$-O-benzyl, -O-$(CH_2)_2$-S(O)-$(CH_2)_2$-O-methyl, -O-$(CH_2)_2$-S(O)-$(CH_2)_2$-O-phenyl, and -O-$(CH_2)_2$-S(O)-$(CH_2)_2$-O-pyridinyl.

Examples of -O-$(CH_2)_p$-S(O_2)-$(CH_2)_p$NR_9R_{10} include -O-$(CH_2)_2$-S(O_2)-$(CH_2)_2$-1-piperidine, -O-$(CH_2)_2$-S(O_2)-$(CH_2)_2$-4-methyl-1-piperazine, -O-$(CH_2)_2$-S(O_2)-$(CH_2)_2$-diethylamine, and -O-$(CH_2)_2$-

$S(O_2)-(CH_2)_2$-4-pyridinyl-1-piperazine.

Examples of $-O-(CH_2)_p-S(O_2)-(CH_2)_p-OR_{15}$ include $-O-(CH_2)_2-S(O_2)-(CH_2)_2$-O-benzyl, $-O-(CH_2)_2-S(O_2)-(CH_2)_2$-O-methyl, $-O-(CH_2)_2-S(O_2)-(CH_2)_2$-O-phenyl, and $-O-(CH_2)_2-S(O_2)-(CH_2)_2-O-$ pyridinyl.

Examples of $-O-(CH_2)_p-[4-[(CH_2)_pOR_{15}]-1$-piperazine] include $-O-(CH_2)_2-[4-[(CH_2)_2OH]-1$-piperazine], $-O-(CH_2)_2-[4-[(CH_2)_2O$benzyl]-1-piperazine], and $-O-(CH_2)_2-[4-[(CH_2)_2O$pyridinylmethyl]-1-piperazine].

Examples of $-O-(CH_2)_p-[4-(CH)(phenyl)_2-1$-piperazine] include $-O-(CH_2)_2-[4-(CH)$(phenyl)(p-chlorophenyl)-1-piperazine], $-O-(CH_2)_2-[4-(CH)(phenyl)_2-1$-piperazine], and $-O-(CH_2)_2-[4-(CH)(p$-fluorophenyl)$_2-1$-piperazine].

Examples of $-O-(CH_2)_p-[4-(CH_2)_q$phenyl-1-piperazine] include $-O-(CH_2)_2-[4-(CH_2)$phenyl-1-piperazine], $-O-(CH_2)_2-[4-(CH_2)_2$phenyl-1-piperazine], and $-O-(CH_2)_2-[4-(CH_2)-m-$trifluoromethylphenyl-1-piperazine].

Examples of $-O-(CH_2)_p-[4-(CH_2)_q$pyridinyl-1-piperazine] include $-O-(CH_2)_2-[4-(CH_2)$pyridinyl-1-piperazine], and $-O-(CH_2)_2-[4-(CH_2)_2$pyridinyl-1-piperazine].

Examples of $-O-(CH_2)_p-[4-(NR_9R_{10}$ substituted pyridinyl)-1-piperazine] include $-O-(CH_2)_2[4-(3$-ethylamino-2-pyridinyl)-1-piperazine, $-O-(CH_2)_2-[4-(3$-piperidinyl-2-pyridinyl)-1-piperazine, and $-O-(CH_2)_2-[4-(3$-amino-2-pyridinyl)-1-piperazine.

Examples of $-O-(CH_2)_p-(OH$ substituted 1-piperidine) include $-O-(CH_2)_2-(4$-hydroxy-1-piperidine) and $-O-(CH_2)_2-(3-$hydroxy-1-piperidine).

Examples of $-O-(CH_2)_p-1$-pyrrolidin-2-one include $-O-(CH_2)_2-$1-pyrrolidin-2-one and $-O-(CH_2)_3-1$-pyrrolidin-2-one.

Examples of optionally substituted piperazines include 2-hydroxymethyl4-methyl-1-piperazine, 2-carboxy-4-phenyl-1-piperazine, 2-methoxy-1-piperazine, 3-methyl-4-phenyl-1-piperazine, and 2-carbomethoxy-4-methyl-1-piperazine.

The tertiary amines and aromatic heterocyclic amines of the subject specification and claims include the N-oxides thereof.

Pharmaceutically acceptable salts means salts useful for

administering the compounds of this invention and include mesylate, hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, maleate malate, succinate, tartrate, and the like. These salts may be in hydrated form.

The compounds of Formula I are all characterized by pronounced antiatherogenic activity, rendering these compounds useful in the treatment and prophylaxis of atherosclerosis.

Various compounds including 2-(4-morpholinyl)-4H-benzopyran-4-one (Cpd #2), 2-(4-morpholinyl)-4H-1,3-benzoxazin-4-one (Cpd #98), 8-methyl-2-(4-morpholinyl)-4H-1,3-benzoxazin-4-one (Cpd #84), 2-(1-(4-thiomorpholinyl))-4H-1,3-benzoxazin-4-one (Cpd #95) and 2-(4-methyl-1-piperazinyl)-4H-1,3-benzoxazin-4-one (Cpd #96) reduced arterial cholesterol accumulation in the SEA Japanese quail model. The reduction in arterial cholesterol was accompanied with reduced serum cholesterol levels with Compounds 84 and 95, but not with Compounds 2, 98 and 96. In normal cholesterolemic SEA Japanese quail, Compound 84 also lowered serum cholesterol. For a description of the Japanese quail model, see Day, C.E. et al., "Utility of a Selected Line (SEA) of the Japanese Quail (Coturnic Coturnix japonica) for the Discovery of New Anti-Atherosclerosis Drugs", Laboratory Animal Science 27:817-821 (1977).

Preferred antiatherosclerotic compounds include Compounds 204, 208, 233, 266, 283, 293, 304, and 326.

In addition, various compounds of Formula I are also potent inhibitors of cell proliferation and are contemplated as useful in the treatment of proliferative diseases such as cancer, rheumatoid arthritis, psoriasis, pulmonary fibrosis, scleroderma, cirrhosis of the liver and for the improved utilization of artificial prosthetic devices such as arterial grafts. These agents may also be useful in the prevention or treatment of obstruction or restenosis of arteries by subsequent administration of drug in cases such as by-pass surgery, coronary by-pass surgery, balloon angioplasty (and other procedures directed at re-establishing patency in occluded or partly occluded vessels, i.e atherectomy, laser or ultrasonic procedures), transplants, and post-thrombotic re-

stenosis.

Compounds of Formula I which are inhibitors of cell proliferation are those active in the test procedure described in Pledger W.J., Stiles C.D., Antniades H.N., Scher C.D., [Proc. Natl. Acad. Sci (USA) (1977). Examples of inhibitors of cell proliferation include Compounds 17, 39, 204, 206, 208, 209, 211-213, 216-219, 221-226, 229, 230, 232-238, 242-250, 253-271, 274-278, 280, 282, 285, 287-297, 299, 303-304, 306-308, 312, 315-316, 320-322, 326, 346, and 348-352.

In addition, various compounds of Formula I are also inhibitors of ADP induced platelet aggregation and are useful in the prevention or treatment of thrombotic diseases and related complications by, for example, inhibition or reversal of platelet aggregation, or platelet adhesion or blood coagulation.

Compounds which are inhibitors of platelet aggregation are those active in the test procedure described in Born, G.R., Cross M.J., J. Physiol., 168, p. 178 (1963). Examples of inhibitiors of ADP induced platelet aggregation include: Compounds 39, 194, 195, 208-217, 219, 223, 239-241, 245-248, 250, 253-255, 257-263, 265, 266, 268-273, 275-282, 285-291, 293-296, 298-303, 308-310, 312, 314-331, 333-346, 347, 348-349, 351, and 352.

Several of these compounds, including compounds 239, 240, 340, 343, 344, 345 and 347, have been found to signficantly inhibit platelet thrombus formation in a canine model of platelet-dependent coronary thrombus formation. Shebuski, R.J., Ramjit, D.R., Bencen, G.H. and Polokoff, M.A. J. Biol. Chem. 264:21550, 1989. Compound 239 accelerates the rate of thrombolysis and prevents reocclusion following successful thrombolysis in a canine model of coronary thrombosis. Shebuski, R.J., Stabilito I.J., Sitko, G.R., and Polokoff, M.H., Circulation 82:169-177, 1990.

In addition, various compounds of Formula I are also potent vasodilators and are useful in the treatment of hypertension, peripheral vascular disease, vascular complications of diabetes and tissue ischemia due to poor blood flow or poor oxygen delivery. Compounds of Formula I which are

vasodilators are those active in the test procedure described in Papadopoulos S.M., Gilbert B.A., Webb R.C., D'Amato C.J. [Neurosurgery 26:2605-2608 (1990)] using phenylephrine and other constricting agents in addition to endothelin. Examples of inhibitors of vasoconstrictors include compounds 194, 208-210, 212, 213, 215, 223-225, 227, 231-234, 237, 243, 250, 254, 255, 257, 259, 263, 268, 269, 271, 278, 279, 281-283, 285, 347-349.

Accordingly, in using compounds of Formula I for the prevention or treatment of atherosclerotic disease or thrombotic diseases, an oral route of administration, either by conventional oral dosage forms or by mixture with food, represents the preferred method of their systemic administration. Alternatively, however, these compounds may be administered by other convenient routes of administration whereby systemic activity is obtained. These other routes of administration would include rectal, vaginal, subcutaneous, intramuscular, intravenous, and like routes.

In using compounds of Formula I for use in angioplasty, an oral route of administration represents the preferred method of their systemic adminstration. Alternatively, however, these compounds may be administered by other convenient routes of administration whereby systemic activity is obtained.

The patient or animal being treated must be given periodic doses of the drug in amounts effective to reduce serum and/or arterial cholesterol, and reduce arterial atherosclerotic lesion size (as determined by angiogram, ultrasound, NMR, etc.); or, by the inhibition or reversal of platelet aggregation, platelet adhesion or blood coagulation; or, by preventing arterial occlusion in vascular trauma associated with procedures such as by-pass grafts, coronary by-passes, angioplasty, post-thrombotic re-stenosis and transplants.

Such effective dosages are readily determined by methods known in the art. For example, small daily doses of the drug (e.g., 0.01-200 mg/kg) may be administered initially with higher succeeding doses until levels of serum and/or arterial cholesterol are favorably affected. By this regimen, a compound of Formula I is administered initially at doses as low

as about 0.01 mg/kg per patient per day, with increasing doses up to about 200 mg/kg per patient per day. In the event the antiatherogenic response in a patient being treated at a dose of 200 mg/kg per day is insufficient, higher doses are also utilized to the extent patient tolerance permits further increases in dose.

While the preferred dosage regimen is with single daily dosing of patients, also preferred for obtaining more uniform serum levels of drug are multiple dosages per day (e.g., up to 4-6 times daily). Accordingly, when 4 daily doses of drug are to be administered, each such dose may be about 50 mg/kg per patient per dose, or higher depending on tolerance.

Similar doses are employed in hon-human mammals, e.g. 0.01-200 mg/kg/day.

Charts A, E, G, I, J, K and L herein describe various methods by which the compounds of Formula I are prepared. With respect to these Charts, X, Y, R_5, R_6, R_7, R_8, R_9 and R_{10} are as defined above.

With respect to Chart A, the compounds of Formula I are prepared by mixing the salicylic acid ester with the morpholine ynamine neat, or in an organic solvent, with stirring. After several minutes, a tertiary amine base, e.g. TEA (triethylamine), is added and the reaction stirred for a period of time. The product can be isolated by recrystallization or column chromatography.

With respect to Chart E, these compounds can be prepared by treatment of a o-hydroxy acetophenone with an iminium salt such as morpholine-4-phosgene iminium chloride, in the presence of boron trifluoride etherate. Subsequent hydrolysis and alkylation yields the desired compounds.

With respect to Chart G, the treatment of an o-hydroxy acetophenone containing a halogen group with an iminium salt such as 4-morpholine dichloromethyleniminium chloride, in the presence of boron trifluoride etherate. Subsequent hydrolysis and alkylation yields the 2-aminochromone. Treatment of the 2-aminochromone with a tetraalkyl tin reagent in the presence of a palladium catalyst such as (bis)triphenylphosphine palladium dichloride and a salt such as lithium chloride affords a 2-

aminochromone substituted with an alkyl substituent.

With respect to Chart I, the compounds of formula I are prepared by treating 4-benzyloxy-2-hydroxy-3-methylacetophenone with sodium hydride, then ethyl α-methylthioacetate and finally acid to yield 7-benzyloxy-8-methyl-2-methylthiomethyl-4H-[1]-benzopyran-4-one. Treatment of that compound with methyl iodide affords the corresponding 7-benzyloxy-8-methyl-2-iodomethyl-4H-[1]-benzopyran-4-one. Treatment of that compound with the appropiate amine then afforded the compounds of formula I. Compounds of formula I were also prepared by treating a formula I compound such as 7-benzyloxy-8-methyl-2-(4-morpholiniylmethyl)-4H-[1]-benzopyran-4-one with a transition metal catalyst in an atmosphere of hydrogen to yield 7-hydroxy-8-methyl-2-(4-morpholiniylmethyl)-4H-[1]-benzopyran-4-one. Alkylation of that phenol with the appropiate group also afforded compounds of formula I.

Alternatively, compounds of formula I can also be prepared by hydrogenation of a R_{5-8} benzyloxy 2-amino-4H-1-benzopyran-4-one followed by alkylation of the resulting phenol as illustrated in chart H.

With respect to Chart J, these compounds are prepared by initial alkylation of the appropriate 2-aminochromone phenol (e.g. prepared according to the methods of Charts D or E) with 1,2-dibromoethane under phase transfer catalysis. Direct substitution of the bromine with an appropriate amine nucleophile affords the 2-aminochromone with a 2-aminoethyloxy substitutent.

With respect to Chart K, these compounds are prepared by treatment of a O-hydroxyacetophenone with potassium t-butoxide and an α-amino acetate, such as methy-2-(4-morpholinyl)-acetate, followed by acidification of the initial adduct.

With respect to Chart L, a procedure for the preparation of 2-aminochromones is contemplated in which a salicylic ester is treated with the anion of an acetyl amine (such as from lithium diisopropyl amide deprotonation of acetyl-4-morpholine) to afford an initial β-ketoamide. This compound, upon cyclodehydration with a reagent such as polyphosphoric ester, would give the 2-aminochromone.

The synthesis of the compounds of the present invention is more completely understood by the following examples:

Relating to Chart A:

Example 17 Preparation of 2-(Morpholinyl)-6-nitro-4H-1-benzopyran-4-one, Compound #17

The ethyl ester of 5-nitro salicylic acid (634 mg, 3.0 mmol) is dissolved in TEA (2.0 mL) and the morpholine ynamine added. The mixture is then stirred for 48 h. The reaction is diluted with EtOAc (200 mL) and washed with water (5 X 25 mL), brine (30 mL) and dried ($MgSO_4$). Evaporation of the solvent yields product which is chromatographed (silica gel [50 g]; 4% EtOH/CH_2Cl_2) to afford 182 mg (22%) of the desired product. MP = 258-9°C; 1H NMR (CDCl3, 300 MHz) 9.05 (d, J = 2.9 Hz, 1 H), 8.44 (dd, J = 8.7, 2.9 Hz, 1 H), 7.46 (d, J = 9.3 Hz, 1 H), 5.69 (s, 1 H), 3.91-3.86 (m, 4 H), 3.61-3.56 (m, 4 H); UV (EtOH) 226 (23,700), 234sh (19,000), 282 (17,600), 316 (15,000); LRMS m/e (rel. intensity) 277 (28), 276 (100), 261 (38), 219 (80), 218 (53), 191 (38), 172 (19), 55 (30), 53 (35), 41 (31); IR (mull) 2954, 2924, 2856, 1637, 1627, 1604, 1565, 1447, 1422, 1347, 1253, 1126, 740, 638; HRMS calc'd. for C13H12N2O5: 276.0746; found: 276.0742; anal calc'd. for C13H12N2O5: C, 56.52, H, 4.38, N, 10.14; found: C, 56.32, H, 4.52, N, 10.16.

Relating to Chart E:

Example 39 Preparation of 7-hydroxy-2-(4-morpholinyl)-8-methyl-4H-1-benzopyran-4-one, Compound 39 (according to Chart E)

Alternate Part A

2',4',-Dihydroxy-3'-methyl-acetophenone (90% purity, 1.108g, 6 mmole) is suspended in 25ml 1,2-dichloroethane and the mixture is treated with boron trifluoride etherate (1.48ml, 12 mmole) while stirring in a 50ml one neck round bottom flask under nitrogen. The mixture is stirred for 30 min at room temperature and is subsequently treated with morpholine-4-phosgene iminium chloride (2.70g, 13.2 mmole). The reaction mixture is warmed to 70°C for 3h. The reaction is cooled to room temperature and the insoluble orange solid is collected by filtration and the filter cake is washed well with

diethylether. The solid is taken up in 25ml acetonitrile in a 50ml one neck round bottom flask under nitrogen and the solution is cooled to 0 C. The mixture is treated with 2.5ml water and the reaction is stirred for 48h as the cooling bath expired. The acetonitrile is removed in vacuo and the residue is carefully diluted with 75ml 2:1 saturated sodium bicarbonate/sodium chloride. The mixture is extracted with 4 X 35ml dichloromethane. The combined organics are dried over magnesium sulfate and are concentrated in vacuo to an amber solid. The solid is washed successively with ethylacetate and diethylether to afford 980mg (44%) of [8-methyl-2-(4-morpholinyl)-4-oxo-4H-1-benzopyran-7-yl]4-morpholinyl carboxylic acid ester (Cpd 100) mp. 232-234°C. The carbamate (945mg, 2.51 mmole) is suspended in 9ml 2/1 methanol/water in a 25ml on neck round bottom flask under nitrogen. The suspension is treated with lithium hydroxide (236mg, 5.62 mmole) and the reaction mixture is stirred for 48h at room temperature. The methanol is removed in vacuo and the pH of the aqueous residue is adjusted to pH = 4.9 by the addition of 5% hydrochloric acid. The precipitated material is collected by filtration and is dried in vacuo at 25 C to afford 569mg (87%) of phenol 39 (mp. > 250 C) as a chalky grayish solid.

Second Alternate Part A

2',4'-Dihydroxy-3'-methyl-acetophenone (90% purity, 18.46g, 100 mmole) is suspended in 50 ml diethylether in a 100 ml one neck round bottom flask under nitrogen. The mixture is treated with boron trifluoride etherate (18.45ml, 150 mmole) and the reaction is stirred overnight at room temperature. The precipitated material is collected by filtration and the filter cake is washed well with fresh diethylether. The filtered material is air dried to afford 10.45g (47%) of difluoroboronate salt as a yellow solid.

The difluoroboronate salt (10.45g, 47 mmole) is combined with morpholine-4-phosgene iminium chloride (21.2g, 104 mmole) in 125ml 1,2-dichloroethane in a 250ml one neck round bottom flask under argon. The reaction mixture is warmed to 70 C for 3h and is cooled to room temperature. The orange-yellow precipitate is collected by filtration and is washed

successively with 1,2-dichloroethane and diethylether to provide 25.3g of an orange solid. The solid is suspended in 200ml acetonitrile in a 500ml one neck round bottom flask and the mixture is cooled to 0 C. The cooled mixture is treated with 20ml water and after stirring 20 min at 0 C, the reaction mixture is stirred overnight at room temperature. The mixture is subsequently cooled to -33 C for 2h and the precipitated hydrochloride salt is collected by filtration and is washed with 125ml ice cold acetonitrile. The filter cake is dried to provide 13.25g (69%) of the carbamate-chromone hydrochloride as a white solid. The filtrate is concentrated in vacuo to an amber syrup. The syrup is diluted with 100ml saturated sodium bicarbonate and the mixture is extracted with 4 X 50ml dichloromethane. The combined organics are dried over magnesium sulfate and are concentrated in vacuo to a reddish oil which upon crystallization with ethylacetate yielded 875mg (5%) of carbamate-chromone as a yellow solid. Hydrolysis of the carbamate-chromone as described in method B affords the desired phenol.

Part B

7-Hydroxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one (0.50g, 1.91mmol) is suspended in 15ml of acetonitrile. 1.3 g of potassium carbonate is added followed by 0.39g (2.1mmol) of alphabromo-p-xylene. The mixture is refluxed for 5 hours. 0.04 g of additional alkylating agent is added and the mixture is refluxed for 2 hours. The cooled mixture is diluted with 5ml of water and filtered. The white solid is washed with water and dried. The solid is recrystallized from ethyl acetate to afford 0.59g (84%) of the product 48 (mp. 167.5-168°C).

Following the general procedure of Example 39 but employing the appropriate hydroxyacetophenone the following products are prepared:

Cpd 216 8-Methyl-7-[(2-methoxy)ethyl]oxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 165-166;

Cpd 219 8-Methyl-7-[(2-thiomethyl)ethyl]oxy-2-(4-Morpholinyl)-4H-1-benzopyran-4-one, mp.

182.5-184;

Cpd 221 8-Methyl-7-[2-(phenylmethoxy)ethyl]oxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one,mp. 155-156;

Cpd 222 7-[2-(Hydroxy)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 267-268;

Cpd 333 7-[2-(2-methoxyethoxy)ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one,mp. 127-128;

Cpd 334 8-methyl-2-(4-morpholinyl)-7-(2-phenoxyethoxy)-4H-1-Benzopyran-4-one, mp. 178-179;

Cpd 251 N-cyclohexyl-N-methyl-2-[[2-(4-morpholinyl)-4-oxo-4H-1-benzopyran-6-yl]oxy]-Acetamide, mp. 168-169;

Cpd 252 2-(4-morpholinyl)-6-(1-naphthalenylmethoxy)-4H-1-Benzopyran-4-one, mp. 205-207;

Cpd 262 8-methyl-2-(4-morpholinyl)-7-[(1-phenyl-1H-tetrazol-5-yl)methoxy]-4H-1-Benzopyran-4-one, mp. 238-241;

Cpd 263 5-[[[8-methyl-2-(4-morpholinyl)-4-oxo-4H-1-benzopyran-7-yl]oxy]methyl]-α-(phenylmethyl)-1H-Tetrazole-1-acetic acid ethyl ester, mp. 61-68;

Cpd 266 7-[[1-(1,1-dimethylethyl)-1H-tetrazol-5-yl]methoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 261-263;

Cpd 271 8-methyl-1-(4-morpholinyl)-7-[[1-(1-phenylethyl)-1H-tetrazol-5-yl]methoxy]-4H-1-Benzopyran-4-one, mp. 181-183;

Cpd 298 7-(acetyloxy)-6-bromo-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 249.5-250.5;

Cpd 299 7-(acetyloxy)-6,8-dimethyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 245-246;

Cpd 300 7-hydroxy-6,8-dimethyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. >300;

Cpd 301 7-(acetyloxy)-6-iodo-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 214-216, dec;

Cpd 302 7-hydroxy-6-iodo-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 243-244, dec;

Cpd 303 6-bromo-7-hydroxy-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 284-285, dec;

Cpd 305 2-(4-morpholinyl)-8-(2-quinolinylmethoxy)-4H-1-Benzopyran-4-one, mp. 247-248;

Cpd 312 2-(4-morpholinyl)-8-(2-propenyloxy)-4H-1-Benzopyran-4-one, mp. 158-159; and

Cpd 286 7-(acetyloxy)-2-(4-morpholinyl)-8-(2-propenyl)-4H-1-Benzopyran-4-one, mp. 183-184.5;

Cpd 287 7-(acetyloxy)-2-(4-morpholinyl)-8-propyl-4H-1-Benzopyran-4-one, mp. 183.5-184.5;

Cpd 288 7-hydroxy-2-(4-morpholinyl)-8-propyl-4H-1-Benzopyran-4-one, mp. 294-297;

Cpd 289 7-[2-(4-methyl-1-piperazinyl)ethoxy]-2-(4-morpholinyl)-8-propyl-4H-1-Benzopyran-4-one, mp. 158-159;

Cpd 290 2-(4-morpholinyl)-8-propyl-7-[2-(1-pyrrolindinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 162-163.5;

Cpd 291 2-(4-morpholinyl)-7-[2-(1-piperidinyl)ethoxy]-8-propyl-4H-1-Benzopyran-4-one, mp. 174-174.75;

Cpd 292 2-(4-morpholinyl)-7-[2-(4-phenyl-1-piperidinyl)ethoxy]-8-propyl-4H-1-Benzopyran-4-one, mp. 142.5-143.5;

Cpd 293 2-(4-morpholinyl)-8-propyl-7-[2-(4-thiomorpholinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 161.5-162;

Cpd 294 (R)-7-[2-[2-(hydroxymethyl)-1-

pyrrolidinyl]ethoxy]-2-(4-morpholinyl)-8-propyl-4H-1-Benzopyran-4-one, mp. 127.5-129;

Cpd 320 7-[2-(4-methyl-1-piperazinyl)ethoxy]-2-2(4-morpholinyl)-8-(2-propenyl)-4H-1-Benzopyran-4-one, mp. 165-165.5;

Cpd 321 2-(4-morpholinyl)-8-(2-propenyl)-7-[2-(1-pyrrolidinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 169.5-171;

Cpd 322 2-(4-morpholinyl)-7-[2-(1-piperidinyl)ethoxy]-8-(2-propenyl)-4H-1-Benzopyran-4-one, mp. 184.5-186;

Cpd 323 2-(4-morpholinyl)-7-[2-(4-phenyl-1-piperidinyl)ethoxy]-8-(2-propenyl)-4H-1-Benzopyran-4-one, mp. 148.5-149;

Cpd 324 2-(4-morpholinyl)-8-(2-propenyl)-7-[2-(4-thiomorpholinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 165-166.5;

Cpd 325 (R)-7-[2-[2-(hydroxymethyl)-1-pyrrolidinyl]ethoxy]-2-(4-morpholinyl)-8-(2-propenyl)-4H-1-Benzopyran-4-one, mp. 136.5-138;

Cpd 348 7-[(1-cyclopropyl-1H-tetrazol-5-yl)methoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 241-242; and

Cpd 349 7-[(1-cyclobutyl-1H-tetrazol-5-yl)methoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 179-181.

Example 83 Preparation of 6-Methyl-2-(4-morpholinyl)-4H-1,3-benzoxazin-4-one, Compound 83

The methyl ester of 5-methylsalicylic acid (2.73 g; 16.4 mmol) is dissolved in acetone (50 ml), cyanogen bromide (1.81g; 17.2 mmol) is added and the solution is cooled to 0°C. Triethylamine (1.73 g; 18.2 mmol) is dissolved in acetone (5 ml) and added dropwise. Precipitation occurred rapidly and the solid is removed by filtration. The filtrate is concentrated in vacuo to afford 3.41 g of the intermediate cyanoether. The cyanoether is dissolved in acetonitrile (50 ,l), morpholine

(1.43 g; 16.4 mmol) is added in 5 ml of acetonitrile and the reaction is stirred for two hours at room temperature. Crystals form and the reaction mixture is cooled to 0°C, and washed with cold acetonitrile to afford 1.65 g (40.8%). Mother liquors are recrystallized from acetonitrile to afford 0.54 g (13.4%); mp. 197-197.9°C; IR (mull) 2955, 2923, 2858, 1674, 1619, 1576, 1466, 1453, 1433, 1424, 1333, 1325, 1315, 1112, 817 cm^{-1}; ^1H-NMR ($CDCl_3$, δ) 7.91 (d, J=1.4 Hz, 1 H, aromatic), 7.40 (d of d's, J=8.3 Hz, 1.9 Hz, 1 H, aromatic), 7.09 (d, J=8.4 Hz, 1 H, aromatic), 3.81 (broad s, 8H, morpholine methylenes), 2.40 (s, 3 H, methyl); UV λ max (ϵ) 217sh(26,550), 223sh(26,350), 259(15,100), 296(4,250), 304sh(3,550); Mass spectrum, ions at m/e (relative intensity) 246(parent, 29), 218(10), 189(20), 134(base, 100), 106(18), 105(10), 78(12), 77(8), 28(19);

Anal. Calc'd. for: $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38.

Found: C, 63.29; H, 5.92; N, 11.31.

Following the general procedure of Example 83, but employing the appropriate o-hydroxy salicylic methyl ester in place of the methyl ester of 5-methylsalicylic acid there are prepared the following product:

Cpd 346 7-Acetoxy-8-methyl-2-(4-morpholinyl)-4H-1,3-benzoxazin-4-one, mp. 263-264.

Example 194 (Relating to Chart G)

Part A

Preparation of 4'-acetoxy-3'-iodo-2'-hydroxy-propiophenone

2',4'-dihydroxy-3'-iodoacetophenone (55.6 g, 0.2 mol) is suspended in 600 ml of methylene chloride. Triethylamine (27.8 ml, 0.2 mol) is added and the cooled mixture (0°C) is treated dropwise with acetyl chloride (16.35 ml, 0.23 mol). The mixture is stirred at 0°C for 1 h and at ambient temperature for 2 h. The mixture is washed with 5% hydrochloric acid, dried owver magnesium sulfate and evaporated. The solid is recrystallized from ethanol to provide 48.39 g of the product.

Part B

Preparation of 7-acetyloxy-8-iodo-2-(4-morpholinyl)-4H-1-benzopyran-4-one (Cpd 194)

4'-Acetoxy-3'-iodo-2'-hydroxy-propiophenone (48.4 g, 0.15

mol) is suspended in 750 ml of ether and treated with boron trifluoride etherate (27.9 ml, 0.22 mol). The mixture is stirred overnight at ambient temperature, filtered and the solid is washed well with ether to afford 47.0 g of the boron difluoride complex. The complex is combined with 4-morpholine dichloromethyleniminium chloride in 400 ml of ethylene dichloride and heated at 70°C for 5 h and at 50°C for 16 h. The reaction is cooled to 0°C and the solid is filtered and washed well with ether (45 g). The solid is suspended in 400 ml of acetonitrile, 40 ml of water is added and the mixture is stirred overnight at room temperature, heated at 50°C for 2 h and finally heated at 60°C for 30 min. The solvent is evaporated and the material is taken up in methylene chloride/ saturated sodium bicarbonate. The aqueous layer is extracted twice with methylene chloride and the combined organics are dried over magnesium sulfate. Evaporation of the solvent and recrystallization from methanol gave 20.8 g (39%) of the chromone. The mother liquors contained 5.8 g of crude product from which a second recrystallization yielded 0.7 g. mp. 201.5-202.5

Part C

Preparation of 8-ethyl-7-hydroxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one

7-Acetyloxy-8-iodo-2-(4-morpholinyl)-4H-1-benzopyran-4-one (2.07 g, 5.0 mmol) is combined with lithium chloride (0.64 g, 15 mmol) tetraethyltin (1.04 ml, 5.25 mmol) and (bis)triphenylphosphine palladium dichloride (70 mg, 0.10 mmol) in 20 ml of dimethylformamide. The mixture is heated a 100°C for 40 min., poured into half saturated sodium chloride and extracted twice with methylene chloride. The organics are washed twice with half saturated sodium chloride, dried over magnesium sulfate and evaporated. The material is taken up in 20 ml of methanol and 10 ml of water and treated with 0.63 g (15 mmol) of lithium hydroxide. The mixture is stirred at room temperature for 30 min. The solvent is evaporated, the mixture is diluted with water and extracted twice with ethyl acetate. The aqueous layer is acidified to pH 6.1 with 5% hydrochloric acid and the solid is filtered, washed with ether and dried to

afford 0.98 g (71%) of the product.

Part D

Preparation of 8-ethyl-2-(4-morpholinyl)-7-(3-pyrindinyl-methoxy)-4H-1-benzopyran-4-one (Cpd 195)

8-Ethyl-7-hydroxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one (0.176 g, 0.64 mmol) and sodium hydride (0.105 g, 60%, 2.6 mmol) are combine in 4 ml of dimethylformamide and heated to 60°C for 20 min. 3-Picoyl chloride hydrochloride (0.321 g, 1.76 mmol) is added and the mixture is heated at 60°C for 1 h. The cooled mixture is poured into 2N sodium hydroxide and ice. The solid is filtered, washed well with water and ether and recrystallzed form ethyl acetate to provide 0.156 g of the product. mp.178-179

Following the general procedure of Example 194, but starting with the 2'-hydroxyacetophonone, there are prepared the following products:

Cpd 217 2-(4-Morpholinyl)-7-phenylmethoxy-8-vinyl-4H-1-benzopyran-4-one, mp. 181-182.5;

Cpd 218 2-(4-Morpholinyl)-8-phenyl-7-phenylmethoxy-4H-1-benzopyran-4-one, mp. 178.5-180.5;

Cpd 273 8-butyl-2-(4-morpholinyl)-7-(phenylmethoxy)-4H-1-Benzopyran-4-one,mp. 142-143;

Cpd 280 8-ethyl-2-(4-morpholinyl)-7-[2-(4-phenyl-1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 178-179;

Cpd 281 (R)-8-ethyl-7-[2-[2-(hydroxymethyl)-1-pyrrolidinyl]ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 127-128.5;

Cpd 282 8-ethyl-2-(4-morpholinyl)-7-[2-(4-thiomorpholinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 151.5-153.5;

Cpd 283 8-ethyl-7-[2-(4-methyl-1-piperazinyl)ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 124-124.5;

Cpd 326 8-ethenyl-7-[2-(4-methyl-1-piperazinyl)ethoxy]-2-(4-morpholinyl)-4H-

1-Benzopyran-4-one, mp. 151-152;

Cpd 327 8-ethenyl-2-(4-morpholinyl)-7-[2-(1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 161-162;

Cpd 328 8-ethenyl-1-(4-morpholinyl)-7-[2-(4-phenyl-1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 169-169.5;

Cpd 329 8-ethenyl-2-(4-morpholinyl)-7-[2-(1-pyrrolidinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 155-156;

Cpd 330 8-ethenyl-2-(4-morpholinyl)-7-[2-(4-thiomorpholinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 210.5-211.5; and

Cpd 331 (R)-8-ethenyl-7-[2-[2-(hydroxymethyl)-1-pyrrolidinyl]ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 115-117

Example 208 Preparation of 7-(2-Bromoethyl)oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one(Relating to Chart J)

Part A

Cpd 39 (13.1g) is suspended in 150ml of 50% sodium hydroxide in a 500ml flask. The mixture is treated successively with 2.8g (8.2 mmol) tetrabutylammonium hydrogen sulfate and 50ml (0.58 mol) of 1,2-dibromoethane. The reaction mixture is warmed to 60°C for 2h and cooled to 0°C. The solid is collected and washed well with 2N NaOH, water and ether. The material is dissolved in chloroform, adsorbed onto 30g of silica gel (230-400 mesh) and chromatographed over 400g silica gel, eluting with 4% methanol/methylene chloride to afford 8.1g (40%) of 7-(2-Bromoethyl)oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 210-211.5°C

Part B

Preparation of 7-[2-(4-Methyl-1-piperazinyl)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one (Cpd 208)

7-(2-Bromoethyl)oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one (4.0g, 10.9 mmol) is suspended in 10ml chloroform and 7ml of N-methyl piperazine is added. The reaction is warmed to reflux for 5h and cooled to room

temperature. The mixture is partitioned between 50ml of 1:1 2N NaOH/saturated NaCl and 25ml of methylene chloride. The combined organics were dried over magnesium sulfate, concentrated in vacuo, and chromatographed over 80g silica gel, eluting with 15% methanol/dichlormethane to afford 3.5g (83%) of cpd 208, mp. 159-159.5, after recrystallization from ethyl acetate.

Following the general procedure of Example 208 (Part B), using the appropriate bromoethyloxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one and employing the appropriate amine, alcohol or sulfide nucleophile, there are prepared the following products:

Cpd 209 7-(2-(2-Hydroxymethylpiperidin-1-yl)ethyl)oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 142-144;

Cpd 210 7-(2-(3-Hydroxymethylpiperidin-1-yl)ethyl)oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 143-145;

Cpd 211 7-(2-(2-Carboethoxypiperidin-1-yl)ethyl)oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 91.5-92.5;

Cpd 212 7-(2-(3-Carboethoxypiperidin-1-yl)ethyl)oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 113-115;

Cpd 213 8-Methyl-7-(2-(2-methylpiperidin-1-yl)ethyl)oxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 108-110;

Cpd 214 7-(2-(3-Carboxypiperidin-1-yl)ethyl)oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 226.5-228.5;

Cpd 215 8-Methyl-2-(4-morpholinyl)-7-[2-(1-piperazinyl)ethyl]oxy-4H-1-benzopyran-4-one, mp. 112-114;

Cpd 220 8-Methyl-2-(4-morpholinyl)-7-[2-(4-(2-hydroxy)ethyl-1-piperazinyl)ethyl]oxy-4H-1-benzopyran-4-one, mp. 192.5-193.5;

Cpd 223 8-Methyl-2-(4-morpholinyl)-7-[2-(2-thiopyrindinyl)ethyl]oxy-4H-1-benzopyran-

4-one, mp. 146-147;

Cpd 224 8-Methyl-2-(4-morpholinyl)-7-[2-(4-thiopyrindinyl)ethyl]oxy-4H-1-benzopyran-4-one, mp. 211.5-212;

Cpd 225 7-[2-(4-(2-Ethoxyphenyl)-1-piperazinyl)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 158-159;

Cpd 226 8-Methyl-7-[2-((1-Methyl-1,3-imidazol-2-yl)thio)ethyl]oxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 170-170.5;

Cpd 227 7-[2-((Bis-N,N'-(2-methoxy)ethoxy)amino)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one,mp. 88-89;

Cpd 228 8-Methyl-7-[2-((4-Methyl-1,2,4-triazol-3-yl)thio)ethyl]oxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 221-221.5;

Cpd 229 7-[2-(N-Ethyl-N'-((2-hydroxy)ethyl)amino)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one,mp. 144-145;

Cpd 230 8-Methyl-7-[2-((1-Methyl-5-tetrazoyl)thio)ethyl]oxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 188.5-189.5;

Cpd 231 8-Methyl-2-(4-morpholinyl)-7-[2-((2-pyrimidinyl)thio)ethyl]oxy-4H-1-benzopyran-4-one, mp. 202.5-203.5;

Cpd 232 8-Methyl-2-(4-morpholinyl)-7-[2-(4-(2-pyridinyl)-1-piperazinyl)ethyl]oxy-4H-1-benzopyran-4-one, mp. 207-208;

Cpd 233 8-Methyl-2-(4-morpholinyl)-7-[2-(4-thiomorpholinyl)ethyl]oxy-4H-1-benzopyran-4-one, mp. 207.5;

Cpd 234 7-[2-((2-(Bis-N,N'-diethylamino)ethyl)thio)ethyl]oxy-8-Methyl-2-(4-morpholinyl)-4H-1-benzopyran-

4-one, mp. 101-103;

Cpd 235 8-Methyl-7-[2-((2-benzoxazolyl)thio)ethyl]oxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 221-222;

Cpd 236 8-Methyl-7-[2-((2-benzothiazolyl)thio)ethyl]oxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 185.5-187;

Cpd 237 7-[2-(4-(3-Ethylamino-pyridin-2-yl)-1-piperazinyl)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 168-169;

Cpd 238 8-Methyl-2-(4-morpholinyl)-7-[2-(pyrrolidinone-1-yl)ethyl]oxy-4H-1-benzopyran-4-one, mp. 144.5-145.5; and

Cpd 335 8-methyl-2-(4-morpholinyl)-7-[2-(phenylthio)ethoxy]-4H-1-Benzopyran-4-one, mp. 158-159;

Cpd 242 2-(4-morpholinyl)-8-[2-(2-pyridinylthio)ethoxy]-4H-1-Benzopyran-4-one, mp. 148-149;

Cpd 243 8-[2-[4-(2-ethoxyphenyl)-1-piperazinyl]ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 133-134;

Cpd 244 8-[2-[4-[3-(ethylamino)-2-pyridinyl]-1-piperazinyl]ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 122-123;

Cpd 245 2-(4-morpholinyl)-8-[2-(1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 127.5-128.5;

Cpd 246 8-methyl-2-(4-morpholinyl)-7-[2-(phenylsulfinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 202-203;

Cpd 247 7-[2-[bis(2-pyridinylmethyl)amino]ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 106-108;

Cpd 248 (S)-7-[2-[2-(hydroxymethyl)-1-

pyrrolidinyl]ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 138-139;

Cpd 249 7-[2-[bis[(4-methoxyphenyl)methyl]amino]ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 117-119;

Cpd 250 8-methyl-2-(4-morpholinyl)-7-[2-(3-thiazolindinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 158-160.5;

Cpd 253 7-[2-[(2-methoxyphenyl)thio]ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 155-156;

Cpd 254 8-methyl-2-(4-morpholinyl)-7-[2-(3-piperidinyloxy)ethoxy]-4H-1-Benzopyran-4-one, mp. 204-205;

Cpd 255 7-[2-(hexahydro-1H-azepin-1-yl)ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 153-154;

Cpd 256 8-methyl-2-(4-morpholinyl)-7-[2-(4-phenyl-1-piperazinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 242.5-243.5;

Cpd 257 8-methyl-2-(4-morpholinyl)-7-[2-(4-phenyl-1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 177-178;

Cpd 258 (R)-7-[2-[2-(hydroxymethyl)-1-pyrrolidinyl]ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 132-134;

Cpd 259 7-[2-(3-hydroxy-1-pyrrolidinyl)ethoxy]-8-methy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 160-161;

Cpd 260 7-[2-[4-(2-chlorophenyl)-1-piperazinyl]ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 171-172;

Cpd 261 2-(4-morpholinyl)-8-[2-(4-phenyl-1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 138-139;

Cpd 268 8-methyl-7-[2-[methyl[2-(2-pyridinyl)ethyl]amino]ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 83-84;

Cpd 269 8-methyl-2-(4-morpholinyl)-7-[2-(2-pyridinyloxy)ethoxy]-4H-1-Benzopyran-4-one, mp. 175-175.5;

Cpd 272 6-chloro-8-methyl-7-[2-(4-methyl-1-piperazinyl)ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 155-156;

Cpd 279 8-ethyl-2-(4-morpholinyl)-7-[2-(1-pyrrolidinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 144-145;

Cpd 285 7-[2-(3,4-dihydro-2(1H)-isoquinolinyl)ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 143-144;

Cpd 295 8-[2-(3,4-dihydro-2(1H)-isoquinolinyl)ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 157-158;

Cpd 296 2-(4-morpholinyl)-8-[2-[4-(phenylmethyl)-1-piperazinyl]ethoxy]-4H-1-Benzopyran-4-one, mp. 151.5-152.5;

Cpd 297 8-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 167-168;

Cpd 304 8-[2-(ethylphenylamino)ethoxyl]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 127-128;

Cpd 306 1-[2-[[2-(4-morpholinyl)-4-oxo-4H-1-benzopyran-8-yl]oxy]ethyl]-3-Piperidinecarboxylic acid ethyl ester, mp. 83-85;

Cpd 307 1-[2-[[2-(4-morpholinyl)-4-oxo-4H-1-benzopyran-8-yl]oxy]ethyl]-2-Piperidinecarboxylic acid ethyl ester, mp. 119-120;

Cpd 309 6,8-dimethyl-7-[2-(4-methyl-1-

piperazinyl)ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 135-136.5;

Cpd 310 6,8-dimethyl-2-(4-morpholinyl)-7-[2-(1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 139.5-140.5;

Cpd 311 6,8-dimethyl-2-(4-morpholinyl)-7-[2-(1-pyrrolindinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 144-145;

Cpd 314 6-iodo-8-methyl-2-(4-morpholinyl)-7-[2-(1-pyrrolidinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 171-172;

Cpd 315 6-iodo-8-methyl-2-(4-morpholinyl)-7-[2-(1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 170-171;

Cpd 316 6-iodo-8-methyl-7-[2-(4-methyl-1-piperazinyl)ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 174-175;

Cpd 317 6-bromo-8-methyl-2-(4-morpholinyl)-7-[2-(1-pyrrolidinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 171-172;

Cpd 318 6-bormo-8-methyl-2-(4-morpholinyl)-7-[2-(1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 175-176;

Cpd 319 6-bromo-8-methyl-7-[2-(4-methyl-1-piperazinyl)ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mp. 162-163;

Cpd 332 2-(4-morpholinyl)-8-[2-(4-thiomorophlinyl)ethoxy]-4H-1-Benzopyran-4-one, mp. 160.5-161.5; and

Cpd 347 7-[2-(4-Ethyl-1-piperazinyl)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mp. 144.5-145.5.

Example 239 Preparation of 7-[2-(4-Methyl-1-piperazinyl)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one, mesylate salt Compound 239

7-[2-(4-Methyl-1-piperazinyl)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one, Cpd 208 (2.0g, 5.16 mmol)

is dissolved in 25ml of methylene chloride under nitrogen. The solution is diluted with 5ml of methanol and treated with 0.335ml (5.16 mmol) of methanesulfonic acid. The mixture is concentrated in vacuo to a residual foam. The foam is crystallized from 25ml of ethyl acetate and allowed to digest overnight. The off-white solid is collected, washed with ether and dried in vacuo for 6h at room temperature and for 24h at 50 C to afford 2.48g (99%) of the title salt (mp. 207.5-208.5)

Following the general procedure of example 239, the following salts were prepared:

Cpd 240 8-Methyl-2-(4-morpholinyl)-7-(2-(1-piperidinyl)ethyl)oxy-4H-1-benzopyran-4-one, mesylate salt, mp. 151-153;

Cpd 241 8-Methyl-2-(4-morpholinyl)-7-(3-pyridinyl)methyl)oxy-4H-1-benzopyran-4-one, mesylate salt, mp. 222-223;

Cpd 336 8-Methyl-2-(4-morpholinyl)-7-(2-pyridinylmethoxy)-4H-1-benzopyran-4-one, mesylate salt, mp. 175-176;

Cpd 337 8-Methyl-2-(4-morpholinyl)-7-(2-pyridinylmethoxy)-4H-1-benzopyran-4-one, bismesylate salt, mp. 211-212;

Cpd 338 8-Methyl-2-(4-morpholinyl)-7-(3-pyrindinylmethoxy)-4H-1-benzopyran-4-one, bismesylate salt, mp. 218-220;

Cpd 339 7-[(1-cyclohexyl-1H-tetrazol-5-yl)methoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mesylate salt, mp. >250;

Cpd 340 8-Methyl-2-(4-morpholinyl)-7-(2-(1-pyrrolidinyl)ethyl)oxy-4H-1-benzopyran-4-one, mesylate salt, mp. 215-217;

Cpd 341 8-Methyl-2-(4-morpholinyl)-7-[2-(1-piperazinyl)ethyl]oxy-4H-1-benzopyran-4-one, mesylate salt, mp. 192-194, dec;

Cpd 342 8-Methyl-2-(4-morpholinyl)-7-[2-(4-thiomorpholinyl)ethyl]oxy-4H-1-benzopyran-4-one, mesylate salt, mp. 191-193;

Cpd 343 8-Methyl-2-(4-morpholinyl)-7-[2-(4-thiomorpholinyl)ethyl]oxy-4H-1-benzopyran-4-one, bismesylate salt, mp. 200-202;

Cpd 344 8-methyl-2-(4-morpholinyl)-7-[2-(3-pyridinyloxy)ethoxy]-4H-1-Benzopyran-4-one, bismesylate salt, mp. 175-177; and

Cpd 345 (R)-7-[2-[2-(hydroxymethyl)-1-pyrrolidinyl]ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one, mesylate salt, mp. 161-162.5.

Example 203 Preparation of 7-phenylmethoxy-2-methyl-thiomethyl-8-methyl-4H-1-benzopyran-4-one, Cpd 203 (Relating to Chart I)

Part A

Sodium hydride (50% oil dispersion washed 3x in hexane, 23.2 g, 0.48 mol) is stirred in THF (195 ml) under nitrogen in a flame dried 2 l three-necked round bottom flask equipped with an addition funnel and a condensor. A solution of the 2-hydroxyacetophenone (25 g, 97.6 mmol) and ethyl α-thiomethyl-acetate (130.4 g, 123 ml, 0.9 mol) in THF (164 ml) is slowly dropped into the sodium hydride slurry. After about half of the reagent solution had been added the reaction is heated with a heating gun until the reaction had begun to reflux on its own. The remainder of the reagent solution is slowly added with stirring. After 10 min at ambient temperature and 1 h 40 min at reflux, the solution is evaporated in vacuo. The solution is transferred to a separatory funnel with methylene chloride/2N HCl and shaken for about 10 min. Extraction with methylene chloride (2x) and drying over magnesium sulfate affords the crude ß-diketone which is not further purified.

A biphasic solution of the ß-dikeone and 6N HCl (250 ml) is stirred at ambient temperature overnight. Extraction with methylene chloride and drying over magnesium sulfate afforded 127.13g of crude material after evaporation of the solvent. Flash chromatography (700 g silica gel, 30-50% EtOAc/hexane) afforded 122 g of a mixture of the starting acetophenone, the thiomethylacetate, and some ß-diketone and 4.94 g Cpd 203 (15%). An analytical sample is recrystallized from

ether/hexane to afford white crystalline title product. mp. 110-114°C.

Part B

Preparation of 7-phenylmethoxy-2-iodomethyl-8-methyl-4H-1-benzopyran-4-one

A solution of Cpd 203 (4.0 g, 12.3 mmol) in methyl iodide (12.5 ml) and CH_2Cl_2 (8 ml) is stirred under reflux. After 3 days, the solution is cooled to 0°C and the yellow precipitate filtered off. The filtrate is evaporated down and the residue flash chromatographed (100 g silica gel, 40% EtOAc/hexane) to afford 1.48 g of 7-phenylmethoxy-2-iodomethyl-8-methyl-4H-1-benzopyran-4-one (30%). An analytical sample is prepared by recrystallization from CH_2Cl_2/EtOAc/hexane to afford white crystalline title product. mp. 144-7°C.

Part C

Preparation of 8-Methyl-2-(4-morpholinylmethyl)-7-(phenylmethoxy)-4H-1-benzopyran-4-one (Cpd 204)

Morpholine (0.21 g, 2.5 mmol) is added to a stirring solution of 7-phenylmethoxy-2-iodomethyl-8-methyl-4H-1-benzopyran-4-one (1.0 g, 2.5 mmol) and triethylamine (0.25 ml, 2.5 mmol) in $CHCl_3$ (12 ml). After stirring at ambient temperature for 2.5 h, the solvent is evaporated <u>in vacuo</u>. The residue is flash chromatographed (100 g silica gel, 50-100% EtOAc/CH_2Cl_2, 45 ml fractions) to afford 0.72 g (79%) of the product. Recrystallization from ether afforded a white solid title product. mp. 130-3°C.

Part D

Preparation of 7-hydroxy-2-(4-morpholinylmethyl)-8-methyl-4H-1-benzopyran-4-one, Cpd 205

Palladium black (140 mg) is added to a solution of the benzyl ether Cpd 204 (0.65 g, 1.78 mmol) in EtOAc (50 ml). After shaking in a Parr hydrogenation apparatus under 50 lbs pressure of hydrogen for 23 h, the catalyst is filtered off through a cintered glass funnel rinsing with EtOAc and MeOH. Evaporation of the solvent afforded 0.49 g of crude material. Flash chromatography (100 g silica gel, 4% MeOH/CH_2Cl_2, 50 ml fractions) afforded 35 mg (5%, fractions 6-7) of the starting material and 0.33 g (68%, fractions 11-16) of the phenol. An

analytical sample is prepared by recrystallization from EtOAc/ether/hexane at 4°C to afford white crystalline title product. mp. 144-6°C;

Part E

Preparation of 7-[(1-cyclohexyl-1H-tetrazol-5-yl)methyoxy]-8-methyl-2-(4-morpholinylmethy)-4H-1-benzopyran-4-one, Cpd 206

A suspension of Cpd 205 (100 mg, 0.36 mmol), 5-(4-chloromethyl)-1-cyclohexyltetrazole [see e.g. Chem. Pharm. Bull. 31, 1151 (1983)] (146 mg, 0.73 mmol), and potassium carbonate (201 mg, 1.45 mmol) in acetonitrile (3 ml) is stirred at 60oC. After 17 h, the reaction mixture is evaporated down and then $CHCl_3$ added. The solids are filtered off and the filtrate evaporated. Flash chromatography of the residue (25 g silica gel, 3% MeOH/CH_2Cl_2, 15 ml fractions) afforded 134 mg (85%, fractions 5-6) of white crystalline title product. mp. 193-5°C.

Example 274 (Relating to chart K) Preparation of 8-Hydroxy-2-(4-morpholinylmethylene)-4H-1-benzopyran-4-one

2',3'-Dihydroxy-acetophenone (7.5g, 49 mmole) is dissolved in 303ml dry tetrahydrofuran in a flame dried 1,000ml three neck round bottom flask under nitrogen. The solution is treated rapidly dropwise with potassium t-butoxide (1.0M/THF) (197ml, 197 mmole) and is mechanically stirred vigorously as methyl-2-(4-morpholinyl)-acetate (10.2g, 64 mmole) is added neat. The reaction mixture is heated at reflux for 48h, is treated with a second lot of methyl-2-(4-morpholinyl)-acetate (7g, 44 mmole), and is stirred an additional 24h at reflux. The reaction is cooled to room temperature, is diluted with 200ml water, and the tetrahydrofuran is removed in vacuo. The pH of the aqueous residue is adjusted to 6.8 with 10% hydrochloric acid and the mixture is extracted with 5 X 100ml dichloromethane. The combined organics are dried over magnesium sulfate and are concentrated in vacuo to a brown solid. The solid is washed with 200ml diethyl ether and is dried to afford 8.8g of a tan solid. The solid is recrystallized twice from ethyl acetate to provide 7.5g (60%)

of the title compound as an off-white solid, mp. 202.5°C.

Example 275 Preparation of 8-Benzyloxy-2-(4-morpholinylmethylene)-4H-1-benzopyran-4-one Cpd 275

8-Hydroxy-2-(4-morpholinylmethylene)-4H-1-benzopyran-4-one (261mg, 1 mmole) is suspended in 7ml acetonitrile in a 25ml one neck round bottom flask under nitrogen. The suspension is treated successively with potassium carbonate (829mg, 6 mmole) and benzyl bromide (150ul, 1.3 mmole) and the reaction mixture is warmed to 70°C for 1h. The mixture is cooled to room temperature and the acetonitrile is removed in vacuo. The residue is washed with 1 X 25ml dichloromethane and the insoluble material is removed by filtration. The filtrate is concentrated in vacuo to a yellow oil. The oil is chromatographed over 15g silica gel (230-400 mesh) eluting with 3% methanol/dichloromethane and collecting 6ml fractions. Fractions 12-27 are combined and concentrated to afford a colorless oil which is crystallized from diethyl ether to provide 246mg (70%) of the title compound as a white solid, mp. 107-107.5°C.

Following the general procedures of examples 203 and 274 there are prepared the following products:

Cpd 264 8-methyl-2-(4-morpholinylmethyl)-7-[[1-(1-phenylethyl)-1H-tetrazol-5-yl]methoxy]-4H-1-Benzopyran-4-one, mp. 145-147;

Cpd 265 8-methyl-2-(4-morpholinylmethyl)-7-[(1-phenyl-1H-tetrazol-5-yl)methoxy]-4H-1-Benzopyran-4-one, mp. 162-163;

Cpd 267 7-[[1-(1,1-dimethylethyl)-1H-tetrazol-5-yl]methoxy]-8-methyl-1-(4-morpholinylmethyl)-4H-1-Benzopyran-4-one, mp. 125-130;

Cpd 270 5-[[[8-methyl-2-(4-morpholinylmethyl)-4-oxo-4H-1-benzopyran-7-yl]oxy]methyl]-α-(pehnylmethyl)-1H-Tetrazole-1-acetic acid ethyl ester, mp. 190-194;

Cpd 276 2-(4-morpholinylmethyl)-8-[[3-(trifluoromethyl)pehnyl]methoxy]-4H-1-Benzopyran-4-one, mp. 124.5-125.5;

Cpd 277 8-[2-(4-methyl-1-piperazinyl)ethoxy]-2-(4-morpholinylmethyl)-4H-1-Benzopyran-4-one, mp. 88.5-89.5;

Cpd 278 8-[2-[4-(2-ethoxyphenyl)-1-piperazinyl]ethoxy]-2-(4-morpholinylmethyl)-4H-1-Benzopyran-4-one, mp. 134.5-135.5;

Cpd 308 2-(4-morpholinyllmethyl)-8-[[1-(1-phenylethyl)-1H-tetrazol-5-yl]methoxy]-4H-1-Benzopyran-4-one, mp. 105-110;

Cpd 350 8-[(1-cyclopropyl-1H-tetrazol-5-yl)methoxy]-2-(4-morpholinylmethyl)-4H-1-Benzopyran-4-one, mp. 84-87;

Cpd 351 7-[(1-cyclobutyl-1H-tetrazol-5-yl)methoxy]-8-methyl-2-(4-morpholinylmethyl)-4H-1-Benzopyran-4-one, mp. 178-179; and

Cpd 352 7-[(1-cyclopropyl-1H-tetrazol-5-yl)methoxy]-8-methyl-2-(4-morpholinylmethyl)-4H-1-Benzopyran-4-one, mp. 146-147.

CHART A

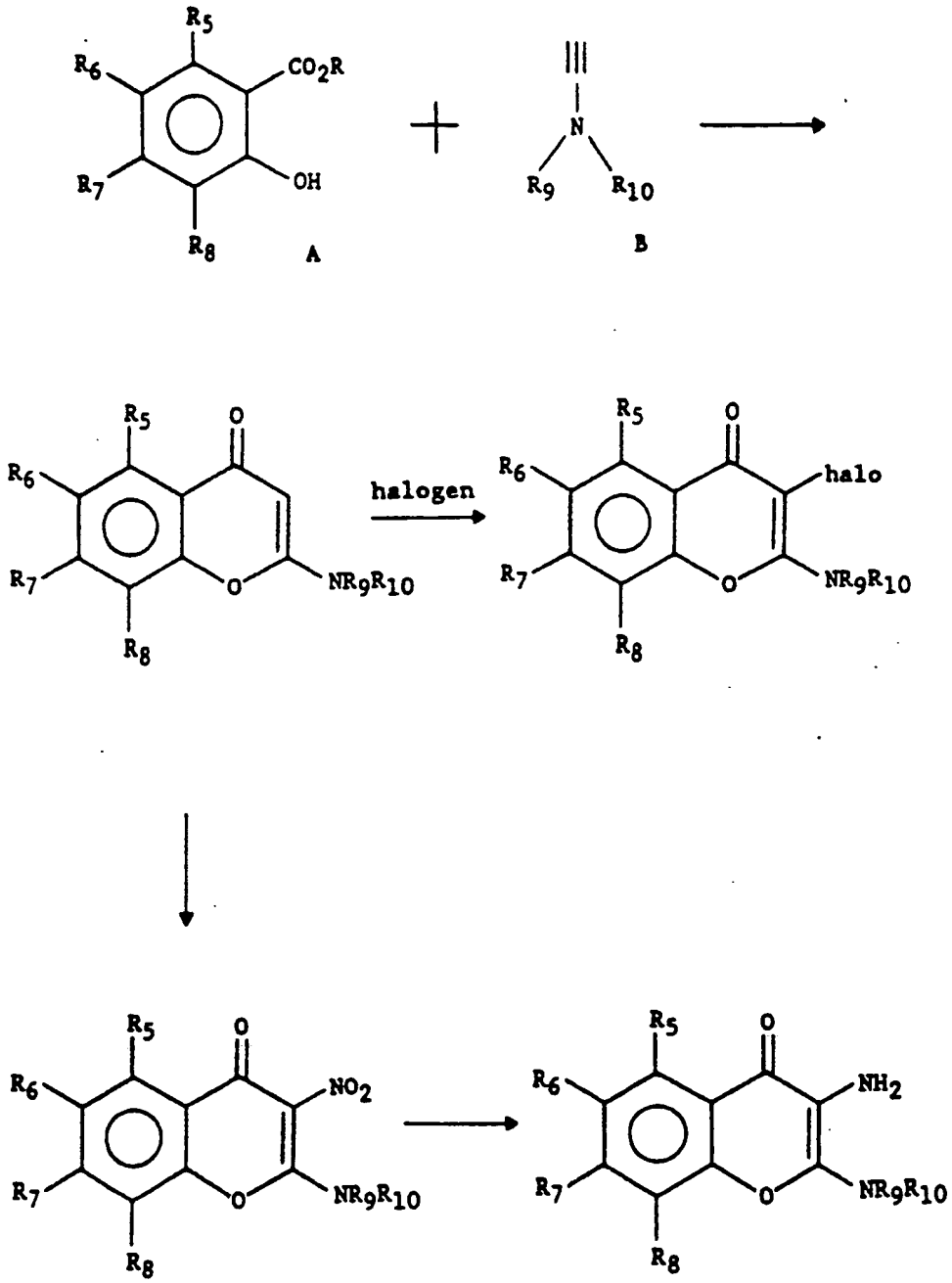


CHART E

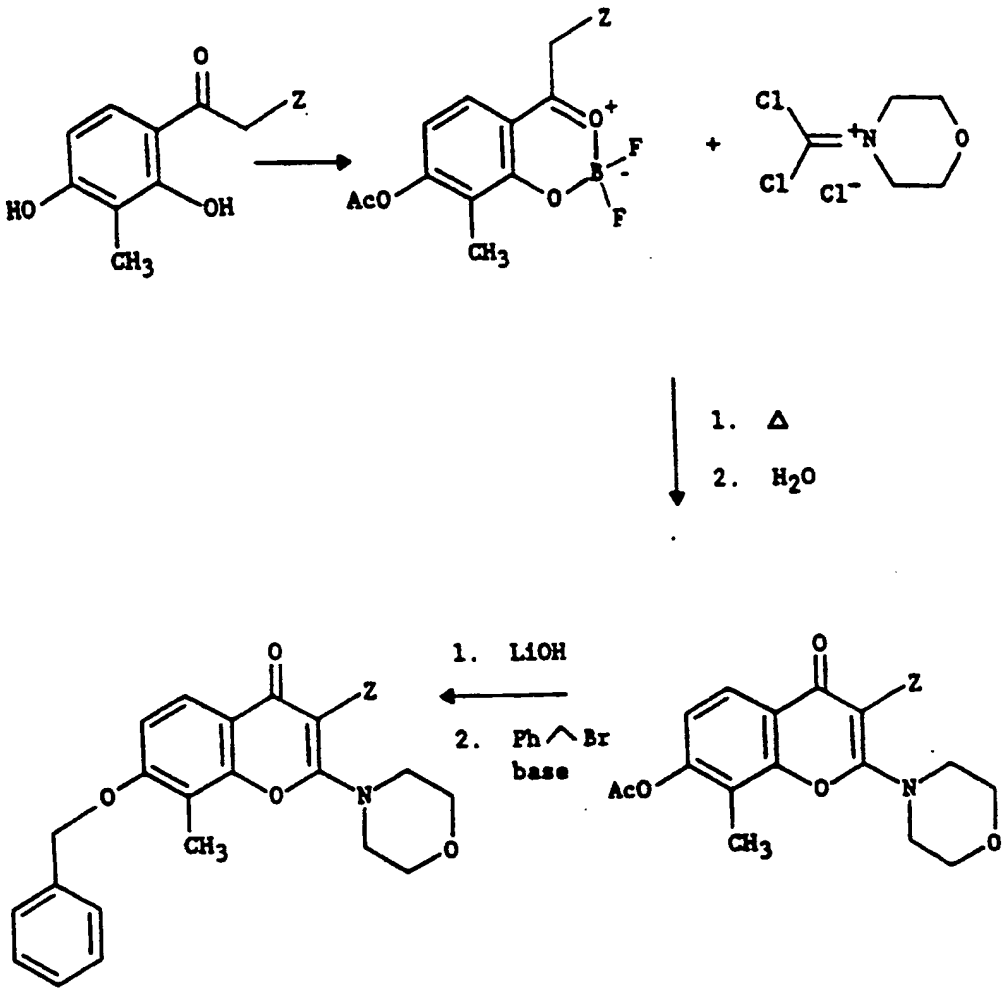
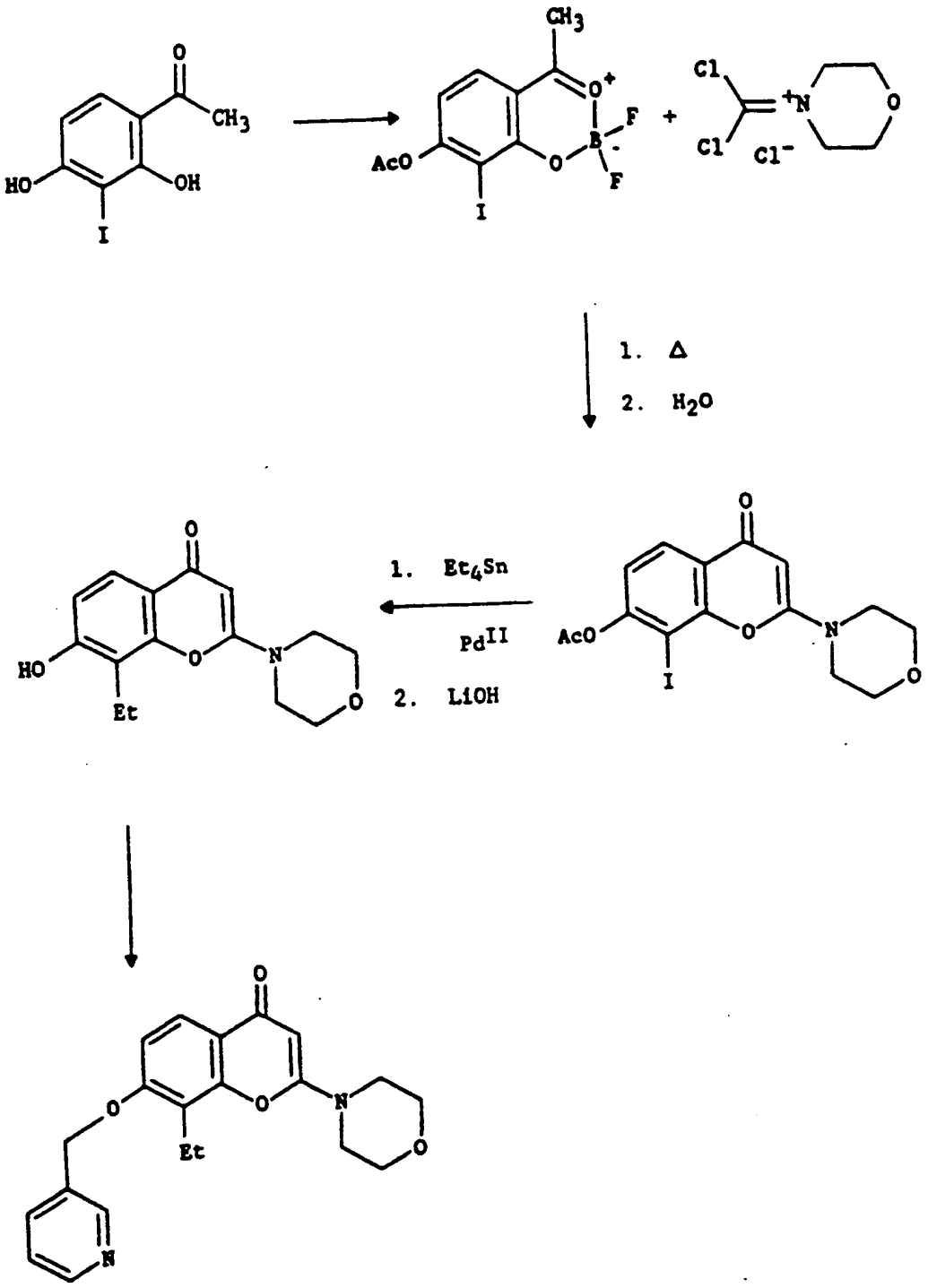


CHART G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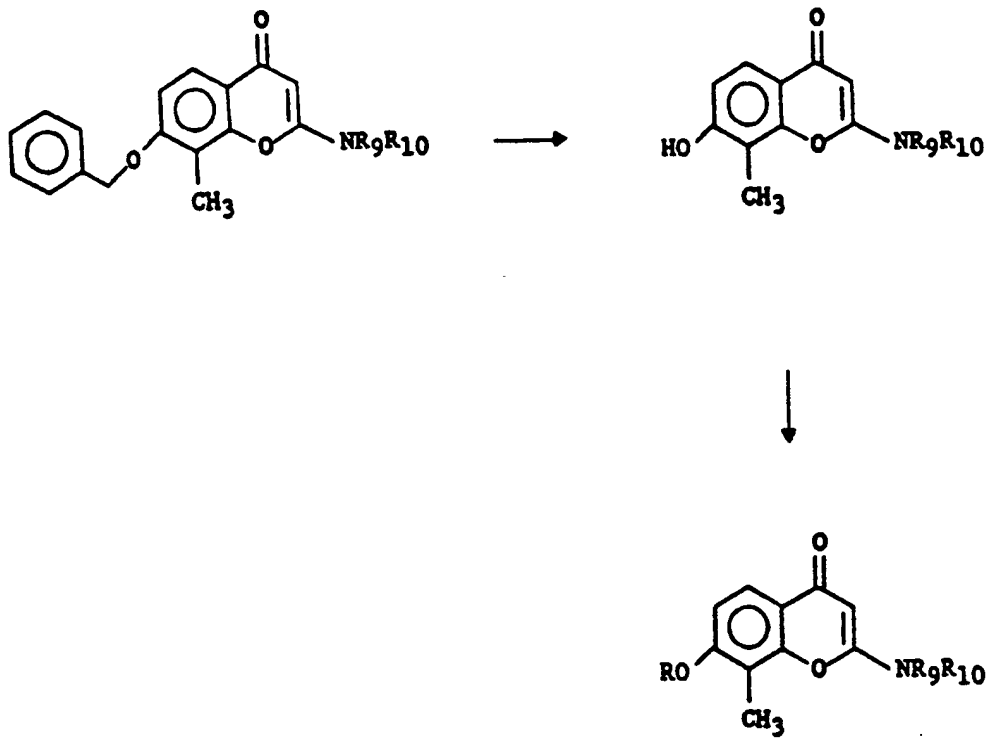
O
CH3
HO
OH
I
AcO
O+
B-
F
F
O
I
Cl
Cl
+N
O
Cl-
1. Δ
2. H2O
AcO
I
1. Et4Sn
PdII
2. LiOH
HO
Et
Et
N
O

CHART H



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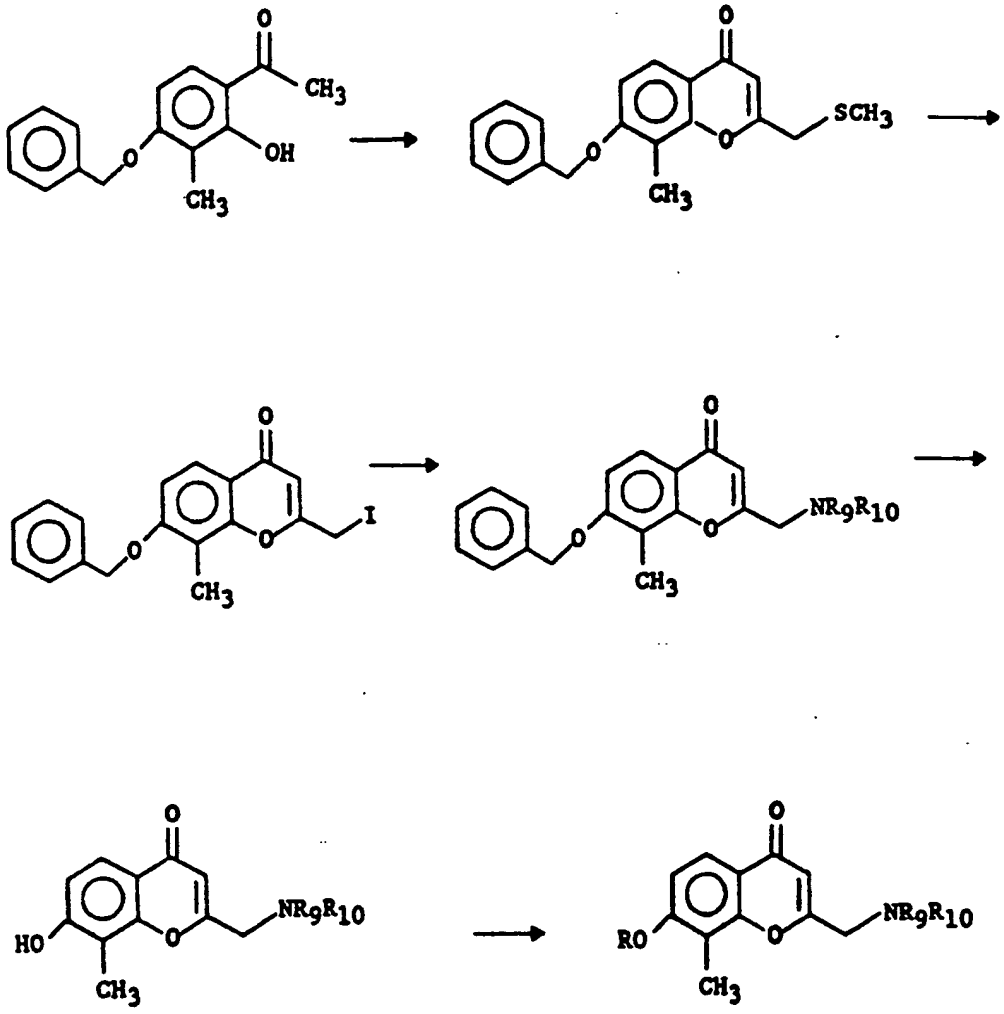

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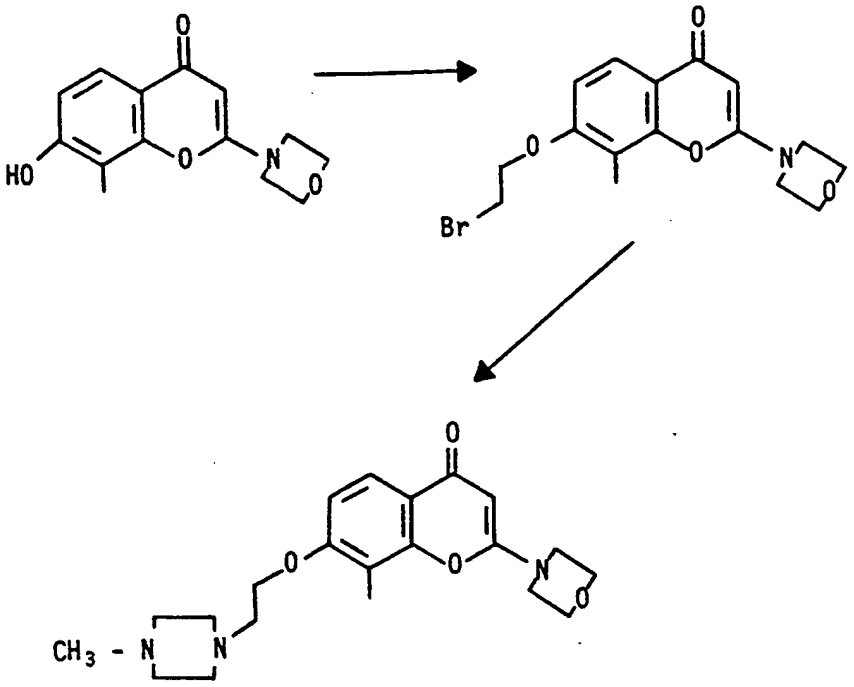

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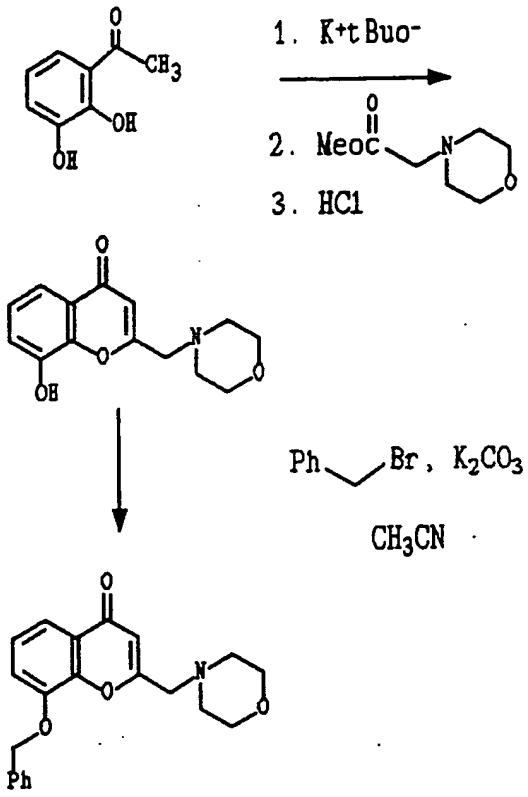

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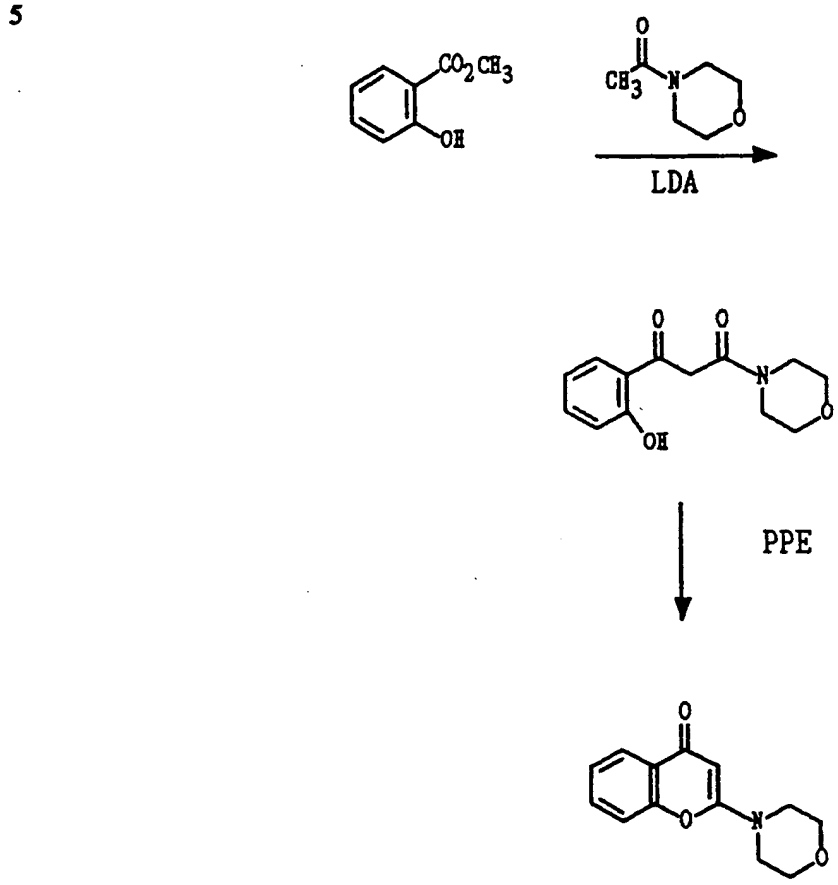
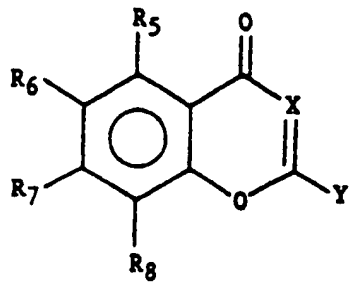


FORMULA



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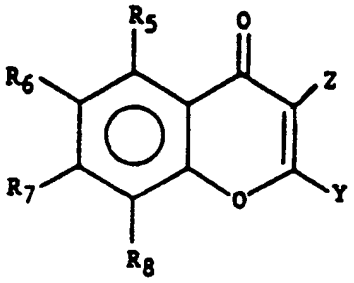

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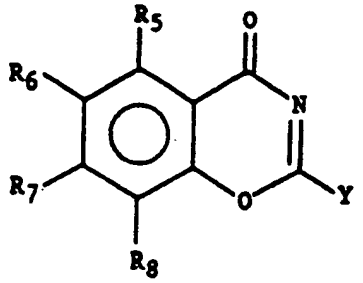

IB

FORMULA (Continued)

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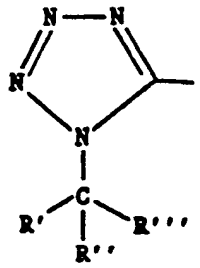
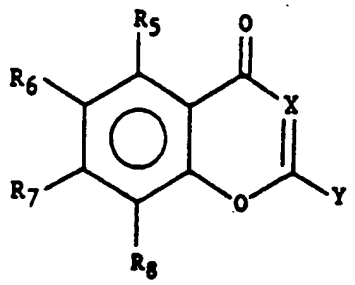


II

CLAIMS

1. A compound of Formula I



wherein X is CZ where Z is H, C_1-C_5 alkyl, amino ($-NH_2$) or a halogen atom;

Y is selected from the group consisting of $-(CH_2)_nNR_9R_{10}$ wherein R_9 and R_{10}, being the same or different, are selected from the group consisting of (a) hydrogen, with the provisio that R_9 and R_{10} are not both hydrogen; (b) C_1-C_{12} alkyl; (c) phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl); (d) $-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], (e) $-(CH_2)_n$pyridinyl or (f) wherein R_9 and R_{10}, taken together with N, form a saturated or unsaturated heterocyclic amine ring selected from the group consisting of

(aa) 4-morpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(bb) 4-thiomorpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(cc) 3-amino-1-pyrrolidine,

(dd) 1-pyrrolidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, $-CH_2OH$, or trifluoromethyl,

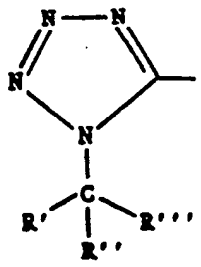
(ee) 1-piperidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-(CH_2)_qOH$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$ or phenyl (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl),

(ff) 1-piperazine, 4-(C_1-C_4alkyl)-1-piperazine, 4-phenyl-1-piperazine (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl) or 4-pyridinyl-1-piperazine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-CH_2O_H$, $-CO_2H$, $-CO_2CH_3$ or $-CO_2CH_2CH_3$, and

(gg) thiazolidine, thiazolidine-4-carboxylic acid, pipecolinic acid, p-piperazinacetophenone, 1-homopiperazine, 1-methylhomopiperazine, 4-phenyl-1,2-3,6-tetrahydropyridine, proline, tetrahydrofurylamine,1-(3-hydroxy)pyrrolidine, nipecotamide, 1,2,3,4-tetrahydroisoquinoline or imidazole;

and R_5, R_6, R_7 and R_8, being the same or different, are selected from the group consisting of hydrogen, C_1-C_8 alkyl, $-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-(CH_2)_n$naphthyl, $-(CH_2)_n$pyridinyl, $-(CH_2)_qNR_9R_{10}$, -CH=CH-phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-CH_2-CH=CH_2$, $-CH=CH-CH_3$, $-CH=CH_2$, $-O-CH_2-CH=CH_2$, $-C\equiv C$-phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-O(CH_2)_p$(N-methylpiperdin-3-yl), $-O-(CH_2)_pNR_9R_{10}$, $-O-CH_2CH(OCH_3)_2$, $-O-(CH_2)_pOR_{15}$, $-O-(CH_2)_p-O-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S-R_{15}$, $-O-(CH_2)_p-O-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O)-R_{15}$, $-O-(CH_2)_p-S(O_2)-R_{15}$,

$-O-(CH_2)_p-S(O)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-[4-[(CH_2)_pOR_{15}]-1-piperazine]$, $-O-(CH_2)_p-[4-(CH)(phenyl)_2-1-piperazine]$ [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)$], $-O-(CH_2)_p-[4-(CH_2)_qphenyl-1-piperazine]$ [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)$], $-O-(CH_2)_p-[4-(CH_2)_qpyridinyl-1-piperazine]$ [pyridinyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl, NR_9R_{10} or $-CO_2(C_1-C_4alkyl)$], $-O-(CH_2)_p-[4-(NR_9R_{10}$ substituted pyridinyl)-1-piperazine, $-O-(CH_2)_p-$(OH substituted 1-piperidine), $-O-(CH_2)_p-1-pyrrolidin-2-one$, $-(CH_2)_nC(O)-(CH_2)_nR_9$, $-(CH_2)_nC(O)O-(CH_2)_pR_9$, $-(CH)_nC(O)O-(CH_2)_pNR_9R_{10}$, $-(CH_2)_nC(O)(CH_2)_nNR_9R_{10}$, NO_2, $-O-(CH_2)_nC(O)-(CH_2)_pR_9$, $-O-(CH_2)_nC(O)O-(CH_2)_pR_9$, $-O-(CH_2)_nC(O)-(CH_2)_nNR_9R_{10}$, $-NR_9R_{10}$, $-N(R_9)(CH_2)_nC(O)-(CH_2)_nR_{10}$, $-N(R_9)-(CH_2)_nC(O)O-(CH_2)_nR_{10}$, $N(R_9)(CH_2)_nC(O)-(CH_2)_nNR_9R_{10}$, $-O-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)$], $-O-(CH_2)_n$pyridine, $-O(CH_2)_nC(O)-(CH_2)_n$pyridine, $-O-(CH_2)_nC(O)O-(CH_2)_n$pyridine, $-O(CH_2)_nC(O)-N(R_9)(CH_2)_n$pyridine, $-O-(CH_2)_n$quinoxalinyl, $-O-(CH_2)_n$quinolinyl, $-O-(CH_2)_n$pyrazinyl, $-O-(CH_2)_n$naphthyl, $-O-(CH_2)_nC(O)-(CH_2)_n$naphthyl, $-O-(CH_2)_nC(O)O-(CH_2)_n$naphthyl, $-O-(CH_2)_nC(O)NR_9-(CH_2)_n$naphthyl, halo (fluoro, chloro, bromo, iodo), OH, $-(CH_2)_q-OH$, $(CH_2)_qOC(O)R_9$, $-(CH_2)_qOC-(O)-NR_9R_{10}$, -(1-cyclohexyl-1H-tetrazol-5-yl)C_1-C_4 alkoxy, $-[1-(C_1-C_5alkyl)-1H-tetrazol-5-yl]C_1-C_4$ alkoxy, $-[1-(phenyl)-1H-tetrazol-5-yl]C_1-C_4$ alkoxy [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)$], $-[1-(pyridinyl)-1H-tetrazol-5-yl]C_1-C_4$ alkoxy, $-[1-(1-phenylethyl)-1H-tetrazol-5-yl]C_1-C_4$ alkoxy, $-C_1-C_4$ alkoxyl, a group of Formula II



wherein R′ is methyl or carboxy, R′′ is hydrogen and R′′′ is selected from benzyl [optionally substituted with one, two or three groups selected from hydroxy, halogen or phenoxy (optionally substituted with one, two or three groups selected from hydroxy or halogen)], C_1-C_5 alkyl, $-(CH_2)_nCO_2H$, $-CH_2SH$, $-CH_2SCH_3$, imidazolinylmethylene, indolinylmethylene, $CH_3CH(OH)$, CH_2OH, $H_2N(CH_2)_4$-(optionally in protected form) or $H_2NC(NH)NH(CH_2)_3$ (optionally in protected form); with the overall proviso that at least one member of R_5, R_6, R_7 or R_8 is selected from the group consisting of $-CH=CH_2$, $-O-(CH_2)_pOH$, $-O-(CH_2)_p-O-(CH_2)_n$pyridin-2-yl, $-O-(CH_2)_p-O-(CH_2)_n$pyridin-3-yl, $-O-(CH_2)_p-O-(CH_2)_n$pyridin-4-yl, $-O-(CH_2)_p-O-(CH_2)_n$-1-(C_1-C_4alkyl)-1H-5-tetrazole, $-O-(CH_2)_p-O-(CH_2)_n$-pyrimidine, $-O-(CH_2)_p-O-(CH_2)_n$-2-benzoxazole, $-O-(CH_2)_p-O-(CH_2)_n$-2-benzothiazole, $-O-(CH_2)_p-O-(CH_2)_n-(C_1-C_4$alkyl)-triazole, $-O-(CH_2)_p-O-(CH_2)_n-(C_1-C_4$alkyl)-imidazole, $-O-(CH_2)_p-O-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S-R_{15}$, $-O-(CH_2)_p-O-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O)-R_{15}$, $-O-(CH_2)_p-S(O_2)-R_{15}$, $-O-(CH_2)_p-S(O)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-[4-[(CH_2)_pOR_{15}]-1$-piperazine], $-O-(CH_2)_p-[4-(CH)(phenyl)_2-1$-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4$alkyl)], $-O-(CH_2)_p-[4-(CH_2)_q$phenyl-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4$alkyl)], $-O-(CH_2)_p-[4-(CH_2)_q$pyridinyl-1-piperazine] [pyridinyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl, NR_9R_{10} or $-CO_2(C_1-C_4$alkyl)], $O-(CH_2)_p-[4-(NR_9R_{10}$ substituted pyridinyl)-1-piperazine, $-O-(CH_2)_p-$(OH substituted 1-piperidine), $-O-(CH_2)_p$-1-pyrrolidin-2-one;

R_{15} is selected from H, C_1-C_5 alkyl, -$(CH_2)_n$phenyl [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or -CO_2(C_1-C_4alkyl)], -$(CH_2)_n$pyridin-1-yl, -$(CH_2)_n$pyridin-2-yl, -$(CH_2)_n$pyridin-3-yl, -$(CH_2)_n$pyridin-4-yl, -$CH_2)_n$-1-(C_1-C_4alkyl)-1H-5-tetrazole, -$(CH_2)_n$-pyrimidine, -$(CH_2)_n$-2-benzoxazole, -$(CH_2)_n$-2-benzothiazole, -$(CH_2)_n$-(C_1-C_4alkyl)-triazole, -$(CH_2)_n$-(C_1-C_4alkyl)-imidazole;

n is 0-5;

p is 2-5;

q is 1-5;

and pharmaceutically acceptable salts and hydrates thereof.

2. A compound according to Claim 1 wherein Y is selected from the group consiting of -$(CH_2)_n$$NR_9R_{10}$ wherein R_9 and R_{10}, taken together with N, form a saturated or unsaturated heterocyclic amine ring selected from the group consisting of:

(aa) 4-morpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(bb) 4-thiomorpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(cc) 3-amino-1-pyrrolidine,

(dd) 1-pyrrolidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, -CH_2OH, or trifluoromethyl,

(ee) 1-piperidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, -$(CH_2)_q$OH, -CO_2H, -CO_2CH_3, -$CO_2CH_2CH_3$ or phenyl (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl),

(ff) 1-piperazine, 4-methyl-1-piperazine, 4-phenyl-1-piperazine (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl) or 4-pyridinyl-1-piperazine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4

alkoxy, halo, trifluoromethyl, $-CH_2OH$, $-CO_2H$, $-CO_2CH_3$ or $-CO_2CH_2CH_3$.

3. A compound according to Claim 1 wherein Z is H or C_1-C_5 alkyl.

4. A compound according to Claim 3 wherein Y is selected from the group consisting of $-(CH_2)_nNR_9R_{10}$ wherein n is 0 or 1, and R_9 and R_{10}, taken together with N, form 4-morpholine.

5. A compound according to Claim 4 wherein Z is H.

6. A compound according to Claim 5 wherein n is 0.

7. A compound according to Claim 2 wherein at least one member selected from R_5, R_6, R_7 or R_8 is selected from: $-O-(CH_2)_p-S-R_{15}$, $-O-(CH_2)_p-[4-(CH)phenyl)_2-1-piperazine]$, $-CH=CH_2$, or $-O-(CH_2)_pO-(CH_2)_pOR_{15}$.

8. A compound according to Claim 1 selected from the group consisting of:

Cpd 217	2-(4-Morpholinyl)-7-phenylmethoxy-8-vinyl-4H-1-benzopyran-4-one;
Cpd 219	8-Methyl-7-[(2-thiomethyl)ethyl]oxy-2-(4-Morpholinyl)-4H-1-benzopyran-4-one;
Cpd 220	8-Methyl-2-(4-morpholinyl)-7-[2-(4-(2-hydroxy)ethyl-1-piperazinyl)ethyl]oxy-4H-1-benzopyran-4-one;
Cpd 222	7-[2-(Hydroxy)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one;
Cpd 223	8-Methyl-2-(4-morpholinyl)-7-[2-(2-thiopyrindinyl)ethyl]oxy-4H-1-benzopyran-4-one;
Cpd 226	8-Methyl-7-[2-((1-Methyl-1,3-imidazol-2-yl)thio)ethyl]oxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one;
Cpd 228	8-Methyl-7-[2-((4-Methyl-1,2,4-triazol-3-yl)thio)ethyl]oxy-2-(4-morpholinyl)-4H-1-

benzopyran-4-one;

Cpd 230 8-Methyl-7-[2-((1-Methyl-5-tetrazoyl)thio)ethyl]oxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one;

Cpd 231 8-Methyl-2-(4-morpholinyl)-7-[2-((2-pyrimidinyl)thio)ethyl]oxy-4H-1-benzopyran-4-one;

Cpd 233 8-Methyl-2-(4-morpholinyl)-7-[2-(4-thiomorpholinyl)ethyl]oxy-4H-1-benzopyran-4-one;

Cpd 234 7-[2-((2-(Bis-N,N'-diethylamino)ethyl)thio)ethyl]oxy-8-Methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one;

Cpd 235 8-Methyl-7-[2-((2-benzoxazolyl)thio)ethyl]oxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one;

Cpd 236 8-Methyl-7-[2-((2-benzothiazolyl)thio)ethyl]oxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one;

Cpd 237 7-[2-(4-(3-Ethylamino-pyridin-2-yl)-1-piperazinyl)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one; and

Cpd 238 8-Methyl-2-(4-morpholinyl)-7-[2-(pyrrolidinone-1-yl)ethyl]oxy-4H-1-benzopyran-4-one;

or a pharmaceutically acceptable salt or hydrate thereof.

9. A compound according to Claim 1 selected from the group consisting of:

Cpd 242 2-(4-morpholinyl)-8-[2-(2-pyridinylthio)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 244 8-[2-[4-[3-(ethylamino)-2-pyridinyl]-1-piperazinyl]ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 246 8-methyl-2-(4-morpholinyl)-7-[2-(phenylsulfinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 253 7-[2-[(2-methoxyphenyl)thio]ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 254 8-methyl-2-(4-morpholinyl)-7-[2-(3-piperidinyloxy)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 296 2-(4-morpholinyl)-8-[2-[4-(phenylmethyl)-1-piperazinyl]ethoxy]-4H-1-Benzopyran-4-one;

Cpd 326 8-ethenyl-7-[2-(4-methyl-1-piperazinyl)ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 327 8-ethenyl-2-(4-morpholinyl)-7-[2-(1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 328 8-ethenyl-1-(4-morpholinyl)-7-[2-(4-phenyl-1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 329 8-ethenyl-2-(4-morpholinyl)-7-[2-(1-pyrrolidinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 330 8-ethenyl-2-(4-morpholinyl)-7-[2-(4-thiomorpholinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 331 (R)-8-ethenyl-7-[2-[2-(hydroxymethyl)-1-pyrrolidinyl]ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 333 7-[2-(2-methoxyethoxy)ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;and

Cpd 335 8-methyl-2-(4-morpholinyl)-7-[2-(phenylthio)ethoxy]-4H-1-Benzopyran-4-one;

or a pharmaceutically acceptable salt or hydrate thereof.

10. A compound selected from the group consisting of:

Cpd 208 7-[2-(4-Methyl-1-piperazinyl)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one;

Cpd 209 7-(2-(2-Hydroxymethylpiperidin-1-

yl)ethyl)oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one;

Cpd 210 7-(2-(3-Hydroxymethylpiperidin-1-yl)ethyl)oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one;

Cpd 211 7-(2-(2-Carboethoxypiperidin-1-yl)ethyl)oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one;

Cpd 212 7-(2-(3-Carboethoxypiperidin-1-yl)ethyl)oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one;

Cpd 213 8-Methyl-7-(2-(2-methylpiperidin-1-yl)ethyl)oxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one;

Cpd 214 7-(2-(3-Carboxypiperidin-1-yl)ethyl)oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one;

Cpd 215 8-Methyl-2-(4-morpholinyl)-7-[2-(1-piperazinyl)ethyl]oxy-4H-1-benzopyran-4-one;

Cpd 216 8-Methyl-7-[(2-methoxy)ethyl]oxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one;

Cpd 218 2-(4-Morpholinyl)-8-phenyl-7-phenylmethoxy-4H-1-benzopyran-4-one;

Cpd 225 7-[2-(4-(2-Ethoxyphenyl)-1-piperazinyl)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one;

Cpd 227 7-[2-((Bis-N,N'-(2-methoxy)ethoxy)amino)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one;

Cpd 229 7-[2-(N-Ethyl-N'-((2-hydroxy)ethyl)amino)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one;

Cpd 232 8-Methyl-2-(4-morpholinyl)-7-[2-(4-(2-pyridinyl)-1-piperazinyl)ethyl]oxy-4H-1-benzopyran-4-one;

Cpd 233 8-Methyl-2-(4-morpholinyl)-7-[2-(4-thiomorpholinyl)ethyl]oxy-4H-1-benzopyran-

4-one;

or a pharmaceutically acceptable salt or hydrate thereof.

11. A compound selected from the group consisting of:

Cpd 243 8-[2-[4-(2-ethoxyphenyl)-1-piperazinyl]ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 245 2-(4-morpholinyl)-8-[2-(1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 247 7-[2-[bis(2-pyridinylmethyl)amino]ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 248 (S)-7-[2-[2-(hydroxymethyl)-1-pyrrolidinyl]ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 249 7-[2-[bis[(4-methoxyphenyl)methyl]amino]ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 250 8-methyl-2-(4-morpholinyl)-7-[2-(3-thiazolindinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 251 N-cyclohexyl-N-methyl-2-[[2-(4-morpholinyl)-4-oxo-4H-1-benzopyran-6-yl]oxy]-Acetamide;

Cpd 252 2-(4-morpholinyl)-6-(1-naphtalenylmethoxy)-4H-1-Benzopyran-4-one;

Cpd 255 7-[2-(hexahydro-1H-azepin-1-yl)ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 256 8-methyl-2-(4-morpholinyl)-7-[2-(4-phenyl-1-piperazinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 257 8-methyl-2-(4-morpholinyl)-7-[2-(4-phenyl-1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 258 (R)-7-[2-[2-(hydroxymethyl)-1-pyrrolidinyl]ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 259 7-[2-(3-hydroxy-1-pyrrolidinyl)ethoxy]-8-methy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 260 7-[2-[4-(2-chlorophenyl)-1-piperazinyl]ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 261 2-(4-morpholinyl)-8-[2-(4-phenyl-1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 262 8-methyl-2-(4-morpholinyl)-7-[(1-phenyl-1H-tetrazol-5-yl)methoxy]-4H-1-Benzopyran-4-one;

Cpd 263 5-[[[8-methyl-2-(4-morpholinyl)-4-oxo-4H-1-benzopyran-7-yl]oxy]methyl]-α-(phenylmethyl)-1H-Tetrazole-1-acetic acid ethyl ester;

Cpd 264 8-methyl-2-(4-morpholinylmethyl)-7-[[1-(1-phenylethyl)-1H-tetrazol-5-yl]methoxy]-4H-1-Benzopyran-4-one;

Cpd 265 8-methyl-2-(4-morpholinylmethyl)-7-[(1-phenyl-1H-tetrazol-5-yl)methoxy]-4H-1-Benzopyran-4-one;

Cpd 266 7-[[1-(1,1-dimethylethyl)-1H-tetrazol-5-yl]methoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 267 7-[[1-(1,1-dimethylethyl)-1H-tetrazol-5-yl]methoxy]-8-methyl-1-(4-morpholinylmethyl)-4H-1-Benzopyran-4-one;

Cpd 268 8-methyl-7-[2-[methyl[2-(2-pyridinyl)ethyl]amino]ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 269 8-methyl-2-(4-morpholinyl)-7-[2-(2-pyridinyloxy)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 270 5-[[[8-methyl-2-(4-morpholinylmethyl)-4-oxo-4H-1-benzopyran-7-yl]oxy]methyl]-α-(pehnylmethyl)-1H-Tetrazole-1-acetic acid ethyl ester;

Cpd 271 8-methyl-1-(4-morpholinyl)-7-[[1-(1-

phenylethyl)-1H-tetrazol-5-yl]methoxy]-4H-1-Benzopyran-4-one;

Cpd 272 6-chloro-8-methyl-7-[2-(4-methyl-1-piperazinyl)ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 273 8-butyl-2-(4-morpholinyl)-7-(phenylmethoxy)-4H-1-Benzopyran-4-one;

Cpd 274 8-Hydroxy-2-(4-morpholinylmethylene)-4H-1-benzopyran-4-one;

Cpd 275 8-Benzyloxy-2-(4-morpholinylmethylene)-4H-1-benzopyran-4-one;

Cpd 276 2-(4-morpholinylmethyl)-8-[[3-(trifluoromethyl)pehnyl]methoxy]-4H-1-Benzopyran-4-one;

Cpd 277 8-[2-(4-methyl-1-piperazinyl)ethoxy]-2-(4-morpholinylmethyl)-4H-1-Benzopyran-4-one;

Cpd 278 8-[2-[4-(2-ethoxyphenyl)-1-piperazinyl]ethoxy]-2-(4-morpholinylmethyl)-4H-1-Benzopyran-4-one;

Cpd 279 8-ethyl-2-(4-morpholinyl)-7-[2-(1-pyrrolidinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 280 8-ethyl-2-(4-morpholinyl)-7-[2-(4-phenyl-1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 281 (R)-8-ethyl-7-[2-[2-(hydroxymethyl)-1-pyrrolidinyl]ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 282 8-ethyl-2-(4-morpholinyl)-7-[2-(4-thiomorpholinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 283 8-ethyl-7-[2-(4-methyl-1-piperazinyl)ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 285 7-[2-(3,4-dihydro-2(1H)-isoquinolinyl)ethoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 286 7-(acetyloxy)-2-(4-morpholinyl)-8-(2-

propenyl)-4H-1-Benzopyran-4-one;

Cpd 287 7-(acetyloxy)-2-(4-morpholinyl)-8-propyl-4H-1-Benzopyran-4-one;

Cpd 288 7-hydroxy-2-(4-morpholinyl)-8-propyl-4H-1-Benzopyran-4-one;

Cpd 289 7-[2-(4-methyl-1-piperazinyl)ethoxy]-2-(4-morpholinyl)-8-propyl-4H-1-Benzopyran-4-one;

Cpd 290 2-(4-morpholinyl)-8-propyl-7-[2-(1-pyrrolindinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 291 2-(4-morpholinyl)-7-[2-(1-piperidinyl)ethoxy]-8-propyl-4H-1-Benzopyran-4-one;

Cpd 292 2-(4-morpholinyl)-7-[2-(4-phenyl-1-piperidinyl)ethoxy]-8-propyl-4H-1-Benzopyran-4-one;

Cpd 293 2-(4-morpholinyl)-8-propyl-7-[2-(4-thiomorpholinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 294 (R)-7-[2-[2-(hydroxymethyl)-1-pyrrolidinyl]ethoxy]-2-(4-morpholinyl)-8-propyl-4H-1-Benzopyran-4-one;

Cpd 295 8-[2-(3,4-dihydro-2(1H)-isoquinolinyl)ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 298 7-(acetyloxy)-6-bromo-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 299 7-(acetyloxy)-6,8-dimethyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 300 7-hydroxy-6,8-dimethyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 301 7-(acetyloxy)-6-iodo-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 302 7-hydroxy-6-iodo-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 303 6-bromo-7-hydroxy-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 304 8-[2-(ethylphenylamino)ethoxyl]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 305 2-(4-morpholinyl)-8-(2-quinolinylmethoxy)-4H-1-Benzopyran-4-one;

Cpd 306 1-[2-[[2-(4-morpholinyl)-4-oxo-4H-1-benzopyran-8-yl]oxy]ethyl]-3-Piperidinecarboxylic acid ethyl ester;

Cpd 307 1-[2-[[2-(4-morpholinyl)-4-oxo-4H-1-benzopyran-8-yl]oxy]ethyl]-2-Piperidinecarboxylic acid ethyl ester;

Cpd 308 2-(4-morpholinyllmethyl)-8-[[1-(1-phenylethyl)-1H-tetrazol-5-yl]methoxy]-4H-1-Benzopyran-4-one;

Cpd 309 6,8-dimethyl-7-[2-(4-methyl-1-piperazinyl)ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 310 6,8-dimethyl-2-(4-morpholinyl)-7-[2-(1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 311 6,8-dimethyl-2-(4-morpholinyl)-7-[2-(1-pyrrolindinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 312 2-(4-morpholinyl)-8-(2-propenyloxy)-4H-1-Benzopyran-4-one;

Cpd 314 6-iodo-8-methyl-2-(4-morpholinyl)-7-[2-(1-pyrrolidinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 315 6-iodo-8-methyl-2-(4-morpholinyl)-7-[2-(1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 316 6-iodo-8-methyl-7-[2-(4-methyl-1-piperazinyl)ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 317 6-bromo-8-methyl-2-(4-morpholinyl)-7-[2-(1-pyrrolidinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 318 6-bormo-8-methyl-2-(4-morpholinyl)-7-[2-(1-piperidinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 319 6-bromo-8-methyl-7-[2-(4-methyl-1-

piperazinyl)ethoxy]-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 320 7-[2-(4-methyl-1-piperazinyl)ethoxy]-2-2(4-morpholinyl)-8-(2-propenyl)-4H-1-Benzopyran-4-one;

Cpd 321 2-(4-morpholinyl)-8-(2-propenyl)-7-[2-(1-pyrrolidinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 322 2-(4-morpholinyl)-7-[2-(1-piperidinyl)ethoxy]-8-(2-propenyl)-4H-1-Benzopyran-4-one;

Cpd 323 2-(4-morpholinyl)-7-[2-(4-phenyl-1-piperidinyl)ethoxy]-8-(2-propenyl)-4H-1-Benzopyran-4-one;

Cpd 324 2-(4-morpholinyl)-8-(2-propenyl)-7-[2-(4-thiomorpholinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 325 (R)-7-[2-[-(hydroxymethoxy)-1-pyrrolidinyl]ethoxy]-2-(4-morpholinyl)-8-(2-propenyl)-4H-1-Benzopyran-4-one;

Cpd 332 2-(4-morpholinyl)-8-[2-(4-thiomorophlinyl)ethoxy]-4H-1-Benzopyran-4-one;

Cpd 334 8-methyl-2-(4-morpholinyl)-7-(2-phenoxyethoxy)-4H-1-Benzopyran-4-one;

Cpd 348 7-[(1-cyclopropyl-1H-tetrazol-5-yl) methoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 349 7-[(1-cyclobutyl-1H-tetrazol-5-yl) methoxy]-8-methyl-2-(4-morpholinyl)-4H-1-Benzopyran-4-one;

Cpd 350 8-[(1-cyclopropyl-1H-tetrazol-5-yl) methoxy]-2-(4-morpholinylmethyl)-4H-1-Benzopyran-4-one;

Cpd 351 7-[(1-cyclobutyl-1H-tetrazol-5-yl) methoxy]-8-methyl-2-(4-morpholinylmethyl)-4H-1-Benzopyran-4-one;

Cpd 352 7-[(1-cyclopropyl-1H-tetrazol-5-yl)

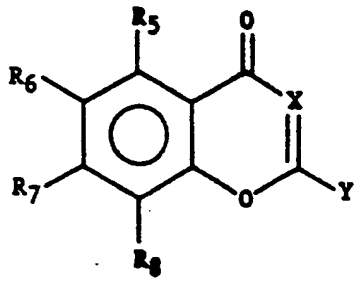
methoxy]-8-methyl-2-(4-morpholinylmethyl)-4H-1-Benzopyran-4-one;

or a pharmaceutically acceptable salt or hydrate thereof.

12. 7-[2-(4-Methyl-1-piperazinyl)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one or a pharmaceutically acceptable salt thereof.

13. 7-[2-(4-Ethyl-1-piperazinyl)ethyl]oxy-8-methyl-2-(4-morpholinyl)-4H-1-benzopyran-4-one or a pharmaceutically acceptable salt thereof.

14. Use of a compound selected from the group consisting of a compound of Formula I



wherein X is N, or CZ where Z is H, C_1-C_5 alkyl, amino ($-NH_2$) or a halogen atom; when X is CZ, Y is selected from the group consisting of $-(CH_2)_nNR_9R_{10}$ wherein R_9 and R_{10}, being the same or different, are selected from the group consisting of

(a) hydrogen, with the provisio that R_9 and R_{10} are not both hydrogen;

(b) C_1-C_{12} alkyl;

(c) phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl);

(d) $-(CH_2)_n$phenyl (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or carboC_1-C_4 alkoxy),

(e) $-(CH_2)_n$pyridinyl or

(f) wherein R_9 and R_{10}, taken together with N, form a saturated or unsaturated heterocyclic amine ring selected from

the group consisting of

(aa) 4-morpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(bb) 4-thiomorpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(cc) 3-amino-1-pyrrolidine,

(dd) 1-pyrrolidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, $-CH_2OH$, or trifluoromethyl,

(ee) 1-piperidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-(CH_2)_qOH$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$ or phenyl (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl),

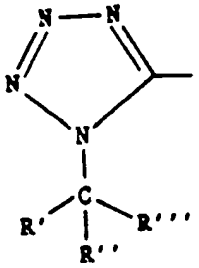
(ff) 1-piperazine, 4-(C_1-C_4alkyl)-1-piperzine, 4-phenyl-1-piperazine (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl) or 4-pyridinyl-1-piperazine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-CH_2OH$, $-CO_2H$, $-CO_2CH_3$ or $-CO_2CH_2CH_3$, and

(gg) thiazolidine, thiazolidine-4-carboxylic acid, pipecolinic acid, p-piperazinacetophenone, 1-homopiperazine, 1-methylhomopiperazine, 4-phenyl-1,2-3,6-tetrahydropyridine, proline, tetrahydrofurylamine, 1-(3-hydroxy)pyrrolidine, nipecotamide, 1,2,3,4-tetrahydroisoquinoline or imidazole;

and R_5, R_6, R_7 and R_8, being the same or different, are selected from the group consisting of hydrogen, C_1-C_8 alkyl, $-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2$(C_1-C_4alkyl)], $-(CH_2)_n$naphthyl, $-(CH_2)_n$pyridinyl, $-(CH_2)_qNR_9R_{10}$, -CH=CH-phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2$(C_1-C_4alkyl)], $-CH_2-CH=CH_2$, $-CH=CH-CH_3$, $-CH=CH_2$, $-O-CH_2-CH=CH_2$, $-C\equiv C$-phenyl [wherein phenyl is

optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or -CO_2(C_1-C_4alkyl)], -O(CH_2)$_p$(N-methylpiperdin-3-yl), -O-(CH_2)$_p$$NR_9R_{10}$, -O-$CH_2CH(OCH_3)_2$, -O-($CH_2$)$_p$$OR_{15}$, -O-($CH_2$)$_p$-O-($CH_2$)$_p$-$OR_{15}$, -O-($CH_2$)$_p$-S-$R_{15}$, -O-($CH_2$)$_p$-O-($CH_2$)$_p$$NR_9R_{10}$, -O-($CH_2$)$_p$-S-($CH_2$)$_p$$NR_9R_{10}$, -O-($CH_2$)$_p$-S-($CH_2$)$_p$-$OR_{15}$, -O-($CH_2$)$_p$-S(O)-$R_{15}$, -O-($CH_2$)$_p$-S($O_2$)-$R_{15}$, -O-($CH_2$)$_p$-S(O)-($CH_2$)$_p$$NR_9R_{10}$, -O-($CH_2$)$_p$-S(O)-($CH_2$)$_p$-$OR_{15}$, -O-($CH_2$)$_p$-S($O_2$)-($CH_2$)$_p$$NR_9R_{10}$, -O-($CH_2$)$_p$-S($O_2$)-($CH_2$)$_p$-$OR_{15}$, -O-($CH_2$)$_p$-[4-[($CH_2$)$_p$$OR_{15}$]-1-piperazine], -O-($CH_2$)$_p$-[4-(CH)(phenyl)$_2$-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or -CO_2(C_1-C_4alkyl)], -O-(CH_2)$_p$-[4-(CH_2)$_q$phenyl-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or -CO_2(C_1-C_4alkyl)], -O-(CH_2)$_p$-[4-(CH_2)$_q$pyridinyl-1-piperazine] [pyridinyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl, NR_9R_{10} or -CO_2(C_1-C_4alkyl)], -O-(CH_2)$_p$-[4-(NR_9R_{10} substituted pyridinyl)-1-piperazine, -O-(CH_2)$_p$-(OH substituted 1-piperidine), -O-(CH_2)$_p$-1-pyrrolidin-2-one, -(CH_2)$_n$C(O)-(CH_2)$_n$$R_9$, -($CH_2$)$_n$C(O)O-($CH_2$)$_p$$R_9$, -($CH_2$)$_n$C(O)O-($CH_2$)$_p$$NR_9R_{10}$, -($CH_2$)$_n$C(O)($CH_2$)$_n$$NR_9R_{10}$, NO_2, -O-(CH_2)$_n$C(O)-(CH_2)$_p$$R_9$, -O-($CH_2$)$_n$C(O)O-($CH_2$)$_p$$R_9$, -O-($CH_2$)$_n$C(O)-($CH_2$)$_n$$NR_9R_{10}$, -$NR_9R_{10}$, -N($R_9$)($CH_2$)$_n$C(O)-($CH_2$)$_n$$R_{10}$, -N($R_9$)-($CH_2$)$_n$C(O)O-($CH_2$)$_n$$R_{10}$, N($R_9$)($CH_2$)$_n$C(O)-($CH_2$)$_n$$NR_9R_{10}$, -O-($CH_2$)$_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or -CO_2(C_1-C_4alkyl)], -O-(CH_2)$_n$pyridine, -O(CH_2)$_n$C(O)-(CH_2)$_n$pyridine, -O-(CH_2)$_n$C(O)O-(CH_2)$_n$pyridine, -O(CH_2)$_n$C(O)-N(R_9)(CH_2)$_n$pyridine, -O-(CH_2)$_n$quinoxalinyl, -O-(CH_2)$_n$quinolinyl, -O-(CH_2)$_n$pyrazinyl, -O-(CH_2)$_n$naphthyl, -O-(CH_2)$_n$C(O)-(CH_2)$_n$naphthyl, -O-(CH_2)$_n$C(O)O-(CH_2)$_n$naphthyl, -O-(CH_2)$_n$C(O)NR_9-(CH_2)$_n$naphthyl, halo (fluoro, chloro, bromo, iodo), OH, -(CH_2)$_q$-OH, (CH_2)$_q$OC(O)R_9, -(CH_2)$_q$OC-(O)-NR_9R_{10}, -(1-cyclohexyl-1H-tetrazol-5-yl)C_1-C_4 alkoxy, -[1-(C_1-C_5alkyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, -[1-(phenyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or -CO_2(C_1-C_4alkyl)], -[1-(pyridinyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, -[1-(1-phenylethyl)-1H-tetrazol-5-

yl]C_1-C_4 alkoxy, -C_1-C_4 alkoxyl, a group of Formula II



wherein R′ is methyl or carboxy, R′′ is hydrogen and R′′′ is selected from benzyl [optionally substituted with one, two or three groups selected from hydroxy, halogen or phenoxy (optionally substituted with one, two or three groups selected from hydroxy or halogen)], C_1-C_5 alkyl, -$(CH_2)_nCO_2H$, -CH_2SH, -CH_2SCH_3, imidazolinylmethylene, indolinylmethylene, $CH_3CH(OH)$, CH_2OH, $H_2N(CH_2)_4$-(optionally in protected form) or $H_2NC(NH)NH(CH_2)_3$ (optionally in protected form); with the overall proviso that at least one member of R_5, R_6, R_7 or R_8 is -$CH=CH_2$, -O-$(CH_2)_pOH$, -O-$(CH_2)_p$-O-$(CH_2)_n$pyridin-2-yl, -O-$(CH_2)_p$-O-$(CH_2)_n$pyridin-3-yl, -O-$(CH_2)_p$-O-$(CH_2)_n$pyridin-4-yl, -O-$(CH_2)_p$-O-$(CH_2)_n$-1-(C_1-C_4alkyl)-1H-5-tetrazole, -O-$(CH_2)_p$-O-$(CH_2)_n$-pyrimidine, -O-$(CH_2)_p$-O-$(CH_2)_n$-2-benzoxazole, -O-$(CH_2)_p$-O-$(CH_2)_n$-2-benzothiazole, -O-$(CH_2)_p$-O-$(CH_2)_n$-(C_1-C_4alkyl)-triazole, -O-$(CH_2)_p$-O-$(CH_2)_n$-(C_1-C_4alkyl)-imidazole, -O-$(CH_2)_p$-O-$(CH_2)_p$-OR_{15}, -O-$(CH_2)_p$-S-R_{15}, -O-$(CH_2)_p$-O-$(CH_2)_pNR_9R_{10}$, -O-$(CH_2)_p$-S-$(CH_2)_pNR_9R_{10}$, -O-$(CH_2)_p$-S-$(CH_2)_p$-OR_{15}, -O-$(CH_2)_p$-S(O)-R_{15}, -O-$(CH_2)_p$-$S(O_2)$-R_{15}, -O-$(CH_2)_p$-S(O)-$(CH_2)_pNR_9R_{10}$, -O-$(CH_2)_p$-S(O)-$(CH_2)_p$-OR_{15}, -O-$(CH_2)_p$-$S(O_2)$-$(CH_2)_pNR_9R_{10}$, -O-$(CH_2)_p$-$S(O_2)$-$(CH_2)_p$-OR_{15}, -O-$(CH_2)_p$-[4-[$(CH_2)_pOR_{15}$]-1-piperazine], -O-$(CH_2)_p$-[4-(CH)$(phenyl)_2$-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or -CO_2(C_1-C_4alkyl)], -O-$(CH_2)_p$-[4-$(CH_2)_q$phenyl-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or -CO_2(C_1-C_4alkyl)], -O-$(CH_2)_p$-[4-$(CH_2)_q$pyridinyl-1-piperazine] [pyridinyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl, NR_9R_{10} or -CO_2(C_1-C_4alkyl)], O-$(CH_2)_p$-[4-(NR_9R_{10} substituted pyridinyl)-1-piperazine, -O-

$(CH_2)_p$-(OH substituted 1-piperidine), -O-$(CH_2)_p$-1-pyrrolidin-2-one;

when X is N, Y is selected from the group consisting of $-NR_9R_{10}$ wherein R_9 and R_{10}, being the same or different, are selected from the group consisting of

(a) hydrogen, with the provisio that R_9 and R_{10} are not both hydrogen;

(b) C_1-C_{12} alkyl;

(c) phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl);

(d) $-(CH_2)_n$phenyl (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or carboC_1-C_4 alkoxy),

(e) $-(CH_2)_n$pyridinyl, or

(f) wherein R_9 and R_{10}, taken together with N, form a saturated or unsaturated heterocyclic amine ring selected from the group consisting of

(aa) 4-morpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(bb) 4-thiomorpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(cc) 3-amino-1-pyrrolidine,

(dd) 1-pyrrolidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, $-CH_2OH$, or trifluoromethyl,

(ee) 1-piperidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-(CH_2)_qOH$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$ or phenyl (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl),

(ff) 1-piperazine, 4-(c_1-C_4alkyl)-1-piperazine, 4-phenyl-1-piperazine (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl) or 4-pyridinyl-1-piperazine optionally

substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-CH_2O_H$, $-CO_2H$, $-CO_2CH_3$ or $-CO_2CH_2CH_3$, and

(gg) thiazolidine, thiazolidine-4-carboxylic acid, pipecolinic acid, p-piperazinacetophenone, 1-homopiperazine, 1-methylhomopiperazine, 4-phenyl-1,2-3,6-tetrahydropyridine, proline, tetrahydrofurylamine, 1-(3-hydroxy)pyrrolidine, nipecotamide, 1,2,3,4-tetrahydroisoquinoline or imidazole;

and R_5, R_6, R_7 and R_8, being the same or different, are selected from the group consisting of hydrogen, C_1-C_8 alkyl, $-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-(CH_2)_n$naphthyl, $-(CH_2)_n$pyridinyl, $-(CH_2)_qNR_9R_{10}$, -CH=CH-phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-CH_2-CH=CH_2$, $-CH=CH-CH_3$, $-CH=CH_2$, $-O-CH_2-CH=CH_2$, -C≡C-phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-O(CH_2)_p$(N-methylpiperdin-3-yl), $-O-(CH_2)_pNR_9R_{10}$, $-O-CH_2CH(OCH_3)_2$, $-O-(CH_2)_pOR_{15}$, $-O-(CH_2)_p-O-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S-R_{15}$, $-O-(CH_2)_p-O-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O)-R_{15}$, $-O-(CH_2)_p-S(O_2)-R_{15}$, $-O-(CH_2)_p-S(O)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-[4-[(CH_2)_pOR_{15}]-1-piperazine]$, $-O-(CH_2)_p-[4-(CH)(phenyl)_2-1-piperazine]$ [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-O-(CH_2)_p-[4-(CH_2)_q$phenyl-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-O-(CH_2)_p-[4-(CH_2)_q$pyridinyl-1-piperazine] [pyridinyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl, NR_9R_{10} or $-CO_2(C_1$-C_4alkyl)], $O-(CH_2)_p-[4-(NR_9R_{10}$ substituted pyridinyl)-1-piperazine, $-O-(CH_2)_p-$(OH substituted 1-piperidine), $-O-(CH_2)_p$-1-pyrrolidin-2-one, $-(CH_2)_nC(O)-(CH_2)_nR_9$, $-(CH_2)_nC(O)O-(CH_2)_pR_9$, $-(CH)_nC(O)O-(CH_2)_pNR_9R_{10}$, $-(CH_2)_nC(O)(CH_2)_nNR_9R_{10}$, NO_2, $-O-(CH_2)_nC(O)-(CH_2)_pR_9$,

$-O-(CH_2)_nC(O)O-(CH_2)_pR_9$, $-O-(CH_2)_nC(O)-(CH_2)_nNR_9R_{10}$, $-NR_9R_{10}$, $-N(R_9)(CH_2)_nC(O)-(CH_2)_nR_{10}$, $-N(R_9)-(CH_2)_nC(O)O-(CH_2)_nR_{10}$, $N(R_9)(CH_2)_nC(O)-(CH_2)_nNR_9R_{10}$, $-O-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)$], $-O-(CH_2)_n$pyridine, $-O(CH_2)_nC(O)-(CH_2)_n$pyridine, $-O-(CH_2)_nC(O)O-(CH_2)_n$pyridine, $-O(CH_2)_nC(O)-N(R_9)(CH_2)_n$pyridine, $-O-(CH_2)_n$quinoxalinyl, $-O-(CH_2)_n$quinolinyl, $-O-(CH_2)_n$pyrazinyl, $-O-(CH_2)_n$naphthyl, $-O-(CH_2)_nC(O)-(CH_2)_n$naphthyl, $-O-(CH_2)_nC(O)O-(CH_2)_n$naphthyl, $-O-(CH_2)_nC(O)NR_9-(CH_2)_n$naphthyl, halo (fluoro, chloro, bromo, iodo), OH, $-(CH_2)_q-OH$, $(CH_2)_qOC(O)R_9$, $-(CH_2)_qOC-(O)-NR_9R_{10}$, -(1-cyclohexyl-1H-tetrazol-5-yl)C_1-C_4 alkoxy, -[1-(C_1-C_5alkyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, -[1-(phenyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)$], -[1-(pyridinyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, -[1-(1-phenylethyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, or $-C_1-C_4$ alkoxyl;

R_{15} is selected from H, C_1-C_5 alkyl, $-(CH_2)_n$phenyl [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)$], $-(CH_2)_n$pyridin-1-yl, $-(CH_2)_n$pyridin-2-yl, $-(CH_2)_n$pyridin-3-yl, $-(CH_2)_n$pyridin-4-yl, $-CH_2)_n-1-(C_1-C_4alkyl)-1H-5-$tetrazole, $-(CH_2)_n-$pyrimidine, $-(CH_2)_n-2-$benzoxazole, $-(CH_2)_n-2-$benzothiazole, $-(CH_2)_n-(C_1-C_4alkyl)-$triazole, $-(CH_2)_n-(C_1-C_4alkyl)-$imidazole;

n is 0-5;

p is 2-5;

q is 1-5;

and pharmaceutically acceptable salts or hydrates thereof; to prepare a medicament for preventing or treating atherosclerosis.

15. The use according to Claim 14 wherein Y is selected from the group consiting of $-(CH_2)_nNR_9R_{10}$ wherein R_9 and R_{10}, taken together with N, form a saturated or unsaturated heterocyclic amine ring selected from the group consisting of:

(aa) 4-morpholine optionally substituted with one or

two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(bb) 4-thiomorpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

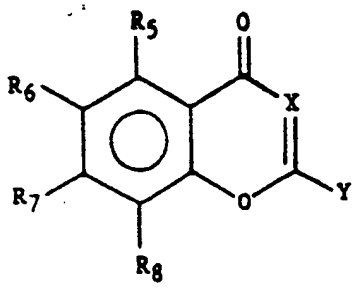
(cc) 3-amino-1-pyrrolidine,

(dd) 1-pyrrolidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, $-CH_2OH$, or trifluoromethyl,

(ee) 1-piperidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-(CH_2)_qOH$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$ or phenyl (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl),

(ff) 1-piperazine, 4-methyl-1-piperazine, 4-phenyl-1-piperazine (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl) or 4-pyridinyl-1-piperazine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-CH_2OH$, $-CO_2H$, $-CO_2CH_3$ or $-CO_2CH_2CH_3$.

16. A pharmaceutical composition comprising a compound selected from the group consisting of compounds of Formula I



wherein X is N, or CZ where Z is H, C_1-C_5 alkyl, amino ($-NH_2$) or a halogen atom;

when X is CZ, Y is selected from the group consisting of $-(CH_2)_nNR_9R_{10}$ wherein R_9 and R_{10}, being the same or different,

are selected from the group consisting of

(a) hydrogen, with the provisio that R_9 and R_{10} are not both hydrogen;

(b) C_1-C_{12} alkyl;

(c) phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl);

(d) $-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)],

(e) $-(CH_2)_n$pyridinyl or

(f) wherein R_9 and R_{10}, taken together with N, form a saturated or unsaturated heterocyclic amine ring selected from the group consisting of

(aa) 4-morpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(bb) 4-thiomorpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(cc) 3-amino-1-pyrrolidine,

(dd) 1-pyrrolidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, $-CH_2OH$, or trifluoromethyl,

(ee) 1-piperidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-(CH_2)_qOH$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$ or phenyl (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl),

(ff) 1-piperazine, 4-(C_1-C_4alkyl)-1-piperazine, 4-phenyl-1-piperazine (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl) or 4-pyridinyl-1-piperazine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-CH_2OH$, $-CO_2H$, $-CO_2CH_3$ or $-CO_2CH_2CH_3$, and

(gg) thiazolidine, thiazolidine-4-carboxylic acid,

pipecolinic acid, p-piperazinacetophenone, 1-homopiperazine, 1-methylhomopiperazine, 4-phenyl-1,2-3,6-tetrahydropyridine, proline, tetrahydrofurylamine, 1-(3-hydroxy)pyrrolidine, nipecotamide, 1,2,3,4-tetrahydroisoquinoline or imidazole;

and R_5, R_6, R_7 and R_8, being the same or different, are selected from the group consisting of hydrogen, C_1-C_8 alkyl, $-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-(CH_2)_n$naphthyl, $-(CH_2)_n$pyridinyl, $-(CH_2)_qNR_9R_{10}$, -CH=CH-phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-CH_2$-CH=CH_2, -CH=CH-CH_3, -CH=CH_2, -O-CH_2-CH=CH_2, -C≡C-phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-O(CH_2)_p$(N-methylpiperdin-3-yl), $-O-(CH_2)_pNR_9R_{10}$, -O-$CH_2CH(OCH_3)_2$, $-O-(CH_2)_pOR_{15}$, $-O-(CH_2)_p-O-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S-R_{15}$, $-O-(CH_2)_p-O-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O)-R_{15}$, $-O-(CH_2)_p-S(O_2)-R_{15}$, $-O-(CH_2)_p-S(O)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-$[4-[$(CH_2)_pOR_{15}$]-1-piperazine], $-O-(CH_2)_p-$[4-(CH)$(phenyl)_2$-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-O-(CH_2)_p-$[4-$(CH_2)_q$phenyl-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-O-(CH_2)_p-$[4-$(CH_2)_q$pyridinyl-1-piperazine] [pyridinyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl, NR_9R_{10} or $-CO_2(C_1$-C_4alkyl)], $-O-(CH_2)_p-$[4-(NR_9R_{10} substituted pyridinyl)-1-piperazine, $-O-(CH_2)_p-$(OH substituted 1-piperidine), $-O-(CH_2)_p$-1-pyrrolidin-2-one, $-(CH_2)_nC(O)-(CH_2)_nR_9$, $-(CH_2)_nC(O)O-(CH_2)_pR_9$, $-(CH_)_nC(O)O-(CH_2)_pNR_9R_{10}$, $-(CH_2)_nC(O)(CH_2)_nNR_9R_{10}$, NO_2, $-O-(CH_2)_nC(O)-(CH_2)_pR_9$, $-O-(CH_2)_nC(O)O-(CH_2)_pR_9$, $-O-(CH_2)_nC(O)-(CH_2)_nNR_9R_{10}$, $-NR_9R_{10}$, $-N(R_9)(CH_2)_nC(O)-(CH_2)_nR_{10}$, $-N(R_9)-(CH_2)_nC(O)O-(CH_2)_nR_{10}$, $N(R_9)(CH_2)_nC(O)-(CH_2)_nNR_9R_{10}$, $-O-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4

alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)$], $-O-(CH_2)_n$pyridine, $-O(CH_2)_nC(O)-(CH_2)_n$pyridine, $-O-(CH_2)_nC(O)O-(CH_2)_n$pyridine, $-O(CH_2)_nC(O)-N(R_9)(CH_2)_n$pyridine, $-O-(CH_2)_n$quinoxalinyl, $-O-(CH_2)_n$quinolinyl, $-O-(CH_2)_n$pyrazinyl, $-O-(CH_2)_n$naphthyl, $-O-(CH_2)_nC(O)-(CH_2)_n$naphthyl, $-O-(CH_2)_nC(O)O-(CH_2)_n$naphthyl, $-O-(CH_2)_nC(O)NR_9-(CH_2)_n$naphthyl, halo (fluoro, chloro, bromo, iodo), OH, $-(CH_2)_q-OH$, $(CH_2)_qOC(O)R_9$, $-(CH_2)_qOC-(O)-NR_9R_{10}$, -(1-cyclohexyl-1H-tetrazol-5-yl)C_1-C_4 alkoxy, -[1-(C_1-C_5alkyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, -[1-(phenyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)$], -[1-(pyridinyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, -[1-(1-phenylethyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, $-C_1-C_4$ alkoxyl, a group of Formula II wherein R′ is methyl or carboxy, R′′ is hydrogen and R′′′ is selected from benzyl [optionally substituted with one, two or three groups selected from hydroxy, halogen or phenoxy (optionally substituted with one, two or three groups selected from hydroxy or halogen)], C_1-C_5 alkyl, $-(CH_2)_nCO_2H$, $-CH_2SH$, $-CH_2SCH_3$, imidazolinylmethylene, indolinylmethylene, $CH_3CH(OH)$, CH_2OH, $H_2N(CH_2)_4$-(optionally in protected form) or $H_2NC(NH)NH(CH_2)_3$ (optionally in protected form); with the overall proviso that at least one member of R_5, R_6, R_7 or R_8 is $-CH=CH_2$, $-O-(CH_2)_pOH$, $-O-(CH_2)_p-O-(CH_2)_n$pyridin-2-yl, $-O-(CH_2)_p-O-(CH_2)_n$pyridin-3-yl, $-O-(CH_2)_p-O-(CH_2)_n$pyridin-4-yl, $-O-(CH_2)_p-O-(CH_2)_n$-1-(C_1-C_4alkyl)-1H-5-tetrazole, $-O-(CH_2)_p-O-(CH_2)_n$-pyrimidine, $-O-(CH_2)_p-O-(CH_2)_n$-2-benzoxazole, $-O-(CH_2)_p-O-(CH_2)_n$-2-benzothiazole, $-O-(CH_2)_p-O-(CH_2)_n-(C_1-C_4alkyl)$-triazole, $-O-(CH_2)_p-O-(CH_2)_n-(C_1-C_4alkyl)$-imidazole, $-O-(CH_2)_p-O-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S-R_{15}$, $-O-(CH_2)_p-O-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O)-R_{15}$, $-O-(CH_2)_p-S(O_2)-R_{15}$, $-O-(CH_2)_p-S(O)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-[4-[(CH_2)_pOR_{15}]-1-piperazine]$, $-O-(CH_2)_p-[4-(CH)(phenyl)_2-1-piperazine]$ [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)$], $-O-(CH_2)_p-[4-(CH_2)_q$phenyl-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl,

C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-O-(CH_2)_p$-[4-$(CH_2)_q$pyridinyl-1-piperazine] [pyridinyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl, NR_9R_{10} or $-CO_2(C_1$-C_4alkyl)], $O-(CH_2)_p$-[4-(NR_9R_{10} substituted pyridinyl)-1-piperazine, $-O-(CH_2)_p$-(OH substituted 1-piperidine), $-O-(CH_2)_p$-1-pyrrolidin-2-one;

when X is N, Y is selected from the group consisting of $-NR_9R_{10}$ wherein R_9 and R_{10}, being the same or different, are selected from the group consisting of (a) hydrogen, with the provisio that R_9 and R_{10} are not both hydrogen; (b) C_1-C_{12} alkyl; (c) phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl); (d) $-(CH_2)_n$phenyl (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or carboC_1-C_4 alkoxy), (e) $-(CH_2)_n$pyridinyl or (f) wherein R_9 and R_{10}, taken together with N, form a saturated or unsaturated heterocyclic amine ring selected from the group consisting of

(aa) 4-morpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(bb) 4-thiomorpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(cc) 3-amino-1-pyrrolidine,

(dd) 1-pyrrolidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, $-CH_2OH$, or trifluoromethyl,

(ee) 1-piperidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-(CH_2)_qOH$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$ or phenyl (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl),

(ff) 1-piperazine, 4-(C_1-C_4alkyl)-1-piperazine, 4-phenyl-1-piperazine (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl) or 4-pyridinyl-1-piperazine optionally

substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-CH_2OH$, $-CO_2H$, $-CO_2CH_3$ or $-CO_2CH_2CH_3$, and

(gg) thiazolidine, thiazolidine-4-carboxylic acid, pipecolinic acid, p-piperazinacetophenone, 1-homopiperazine, 1-methylhomopiperazine, 4-phenyl-1,2-3,6-tetrahydropyridine, proline, tetrahydrofurylamine, 1-(3-hydroxy)pyrrolidine, nipecotamide, 1,2,3,4-tetrahydroisoquinoline or imidazole;

and R_5, R_6, R_7 and R_8, being the same or different, are selected from the group consisting of hydrogen, C_1-C_8 alkyl, $-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-(CH_2)_n$naphthyl, $-(CH_2)_n$pyridinyl, $-(CH_2)_qNR_9R_{10}$, -CH=CH-phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-CH_2-CH=CH_2$, $-CH=CH-CH_3$, $-CH=CH_2$, $-O-CH_2-CH=CH_2$, -C≡C-phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-O(CH_2)_p$(N-methylpiperdin-3-yl), $-O-(CH_2)_pNR_9R_{10}$, $-O-CH_2CH(OCH_3)_2$, $-O-(CH_2)_pOR_{15}$, $-O-(CH_2)_p-O-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S-R_{15}$, $-O-(CH_2)_p-O-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O)-R_{15}$, $-O-(CH_2)_p-S(O_2)-R_{15}$, $-O-(CH_2)_p-S(O)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-[4-[(CH_2)_pOR_{15}]-1-piperazine]$, $-O-(CH_2)_p-[4-(CH)(phenyl)_2-1-piperazine]$ [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-O-(CH_2)_p-[4-(CH_2)_q$phenyl-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-O-(CH_2)_p-[4-(CH_2)_q$pyridinyl-1-piperazine] [pyridinyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl, NR_9R_{10} or $-CO_2(C_1$-C_4alkyl)], $O-(CH_2)_p-[4-(NR_9R_{10}$ substituted pyridinyl)-1-piperazine, $-O-(CH_2)_p-(OH$ substituted 1-piperidine), $-O-(CH_2)_p-1$-pyrrolidin-2-one, $-(CH_2)_nC(O)-(CH_2)_nR_9$, $-(CH_2)_nC(O)O-(CH_2)_pR_9$, $-(CH_2)_nC(O)O-(CH_2)_pNR_9R_{10}$, $-(CH_2)_nC(O)(CH_2)_nNR_9R_{10}$, NO_2, $-O-(CH_2)_nC(O)-(CH_2)_pR_9$,

$-O-(CH_2)_nC(O)O-(CH_2)_pR_9$, $-O-(CH_2)_nC(O)-(CH_2)_nNR_9R_{10}$, $-NR_9R_{10}$, $-N(R_9)(CH_2)_nC(O)-(CH_2)_nR_{10}$, $-N(R_9)-(CH_2)_nC(O)O-(CH_2)_nR_{10}$, $N(R_9)(CH_2)_nC(O)-(CH_2)_nNR_9R_{10}$, $-O-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4$alkyl)], $-O-(CH_2)_n$pyridine, $-O(CH_2)_nC(O)-(CH_2)_n$pyridine, $-O-(CH_2)_nC(O)O-(CH_2)_n$pyridine, $-O(CH_2)_nC(O)-N(R_9)(CH_2)_n$pyridine, $-O-(CH_2)_n$quinoxalinyl, $-O-(CH_2)_n$quinolinyl, $-O-(CH_2)_n$pyrazinyl, $-O-(CH_2)_n$naphthyl, $-O-(CH_2)_nC(O)-(CH_2)_n$naphthyl, $-O-(CH_2)_nC(O)O-(CH_2)_n$naphthyl, $-O-(CH_2)_nC(O)NR_9-(CH_2)_n$naphthyl, halo (fluoro, chloro, bromo, iodo), OH, $-(CH_2)_q-OH$, $(CH_2)_qOC(O)R_9$, $-(CH_2)_qOC(O)-NR_9R_{10}$, $-$(1-cyclohexyl-1H-tetrazol-5-yl)C_1-C_4 alkoxy, $-[1-(C_1-C_5$alkyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, $-[1-$(phenyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4$alkyl)], $-[1-$(pyridinyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, $-[1-$(1-phenylethyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, or $-C_1-C_4$ alkoxyl;

with the overall proviso that at least one member of R_5, R_6, R_7, or R_8 is $-CH=CH_2$, $-O-(CH_2)_pOH$, $-O-(CH_2)_p-O-(CH_2)_n$pyridin-2-yl, $-O-(CH_2)_p-O-(CH_2)_n$pyridin-3-yl, $-O-(CH_2)_p-O-(CH_2)_n$pyridin-4-yl, $-O-(CH_2)_p-O-(CH_2)_n-1-(C_1-C_4$alkyl)-1H-5-tetrazole, $-O-(CH_2)_p-O-(CH_2)_n$-pyrimidine, $-O-(CH_2)_p-O-(CH_2)_n$-2-benzoxazole, $-O-(CH_2)_p-O-(CH_2)_n$-2-benzothiazole, $-O-(CH_2)_p-O-(CH_2)_n-(C_1-C_4$alkyl)-triazole, $-O-(CH_2)_p-O-(CH_2)_n-(C_1-C_4$alkyl)-imidazole, $-O-(CH_2)_p-O-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S-R_{15}$, $-O-(CH_2)_p-O-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O)-R_{15}$, $-O-(CH_2)_p-S(O_2)-R_{15}$, $-O-(CH_2)_p-S(O)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-[4-[(CH_2)_pOR_{15}]$-1-piperazine], $-O-(CH_2)_p-[4-(CH)(phenyl)_2-1-$piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4$alkyl)], $-O-(CH_2)_p-[4-(CH_2)_q$phenyl-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4$alkyl)], $-O-(CH_2)_p-[4-(CH_2)_q$pyridinyl-1-piperazine] [pyridinyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo,

OH, trifluoromethyl, NR_9R_{10} or $-CO_2(C_1-C_4alkyl)$], $O-(CH_2)_p$-[4-(NR_9R_{10} substituted pyridinyl)-1-piperazine, $-O-(CH_2)_p$-(OH substituted 1-piperidine), $-O-(CH_2)_p$-1-pyrrolidin-2-one;

R_{15} is selected from H, C_1-C_5 alkyl, $-(CH_2)_n$phenyl [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)$], $-(CH_2)_n$pyridin-1-yl, $-(CH_2)_n$pyridin-2-yl, $-(CH_2)_n$pyridin-3-yl, $-(CH_2)_n$pyridin-4-yl, $-CH_2)_n-1-(C_1-C_4alkyl)-1H-5-tetrazole$, $-(CH_2)_n$-pyrimidine, $-(CH_2)_n$-2-benzoxazole, $-(CH_2)_n$-2-benzothiazole, $-(CH_2)_n-(C_1-C_4alkyl)$-triazole, $-(CH_2)_n-(C_1-C_4alkyl)$-imidazole;

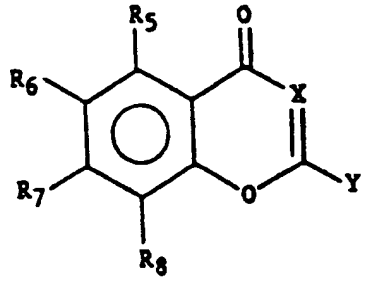
n is 0-5;

p is 2-5;

q is 1-5;

and pharmaceutically acceptable salts and hydrates thereof, in association with a pharmaceutcal carrier.

17. A process for the preparation of a compound of Formula I



wherein X is CZ where Z is H, C_1-C_5 alkyl, amino ($-NH_2$) or a halogen atom;

Y is selected from the group consisting of $-(CH_2)_nNR_9R_{10}$ wherein R_9 and R_{10}, being the same or different, are selected from the group consisting of

(a) hydrogen, with the provisio that R_9 and R_{10} are not both hydrogen;

(b) C_1-C_{12} alkyl;

(c) phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)$;

(d) $-(CH_2)_n$phenyl (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or carboC_1-C_4 alkoxy),

(e) $-(CH_2)_n$pyridinyl or (f) wherein R_9 and R_{10}, taken together with N, form a saturated or unsaturated heterocyclic amine ring selected from the group consisting of

(aa) 4-morpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(bb) 4-thiomorpholine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl,

(cc) 3-amino-1-pyrrolidine,

(dd) 1-pyrrolidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, $-CH_2OH$, or trifluoromethyl,

(ee) 1-piperidine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-(CH_2)_qOH$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$ or phenyl (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl),

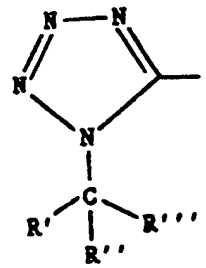
(ff) 1-piperazine, 4-methyl-1-piperazine, 4-phenyl-1-piperazine (wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or trifluoromethyl) or 4-pyridinyl-1-piperazine optionally substituted with one or two members selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, trifluoromethyl, $-CH_2OH$, $-CO_2H$, $-CO_2CH_3$ or $-CO_2CH_2CH_3$, and

(gg) thiazolidine, thiazolidine-4-carboxylic acid, pipecolinic acid, p-piperazinacetophenone, 1-homopiperazine, 1-methylhomopiperazine, 4-phenyl-1,2-3,6-tetrahydropyridine, proline, tetrahydrofurylamine, 1-(3-hydroxy)pyrrolidine, nipecotamide, 1,2,3,4-tetrahydroisoquinoline or imidazole;

and R_5, R_6, R_7 and R_8, being the same or different, are selected from the group consisting of hydrogen, C_1-C_8 alkyl, $-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl

or $-CO_2(C_1-C_4alkyl)]$, $-(CH_2)_n$naphthyl, $-(CH_2)_n$pyridinyl, $-(CH_2)_qNR_9R_{10}$, -CH=CH-phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)]$, $-CH_2-CH=CH_2$, $-CH=CH-CH_3$, $-CH=CH_2$, $-O-CH_2-CH=CH_2$, -C≡C-phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)]$, $-O(CH_2)_p$(N-methylpiperdin-3-yl), $-O-(CH_2)_pNR_9R_{10}$, $-O-CH_2CH(OCH_3)_2$, $-O-(CH_2)_pOR_{15}$, $-O-(CH_2)_p-O-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S-R_{15}$, $-O-(CH_2)_p-O-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O)-R_{15}$, $-O-(CH_2)_p-S(O_2)-R_{15}$, $-O-(CH_2)_p-S(O)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_pNR_9R_{10}$, $-O-(CH_2)_p-S(O_2)-(CH_2)_p-OR_{15}$, $-O-(CH_2)_p-[4-[(CH_2)_pOR_{15}]-1-piperazine]$, $-O-(CH_2)_p-[4-(CH)(phenyl)_2-1-piperazine]$ [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)]$, $-O-(CH_2)_p-[4-(CH_2)_q$phenyl-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)]$, $-O-(CH_2)_p-[4-(CH_2)_q$pyridinyl-1-piperazine] [pyridinyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl, NR_9R_{10} or $-CO_2(C_1-C_4alkyl)]$, $O-(CH_2)_p-[4-(NR_9R_{10}$ substituted pyridinyl)-1-piperazine, $-O-(CH_2)_p-$(OH substituted 1-piperidine), $-O-(CH_2)_p-1-$pyrrolidin-2-one, $-(CH_2)_nC(O)-(CH_2)_nR_9$, $-(CH_2)_nC(O)O-(CH_2)_pR_9$, $-(CH_)_nC(O)O-(CH_2)_pNR_9R_{10}$, $-(CH_2)_nC(O)(CH_2)_nNR_9R_{10}$, NO_2, $-O-(CH_2)_nC(O)-(CH_2)_pR_9$, $-O-(CH_2)_nC(O)O-(CH_2)_pR_9$, $-O-(CH_2)_nC(O)-(CH_2)_nNR_9R_{10}$, $-NR_9R_{10}$, $-N(R_9)(CH_2)_nC(O)-(CH_2)_nR_{10}$, $-N(R_9)-(CH_2)_nC(O)O-(CH_2)_nR_{10}$, $N(R_9)(CH_2)_nC(O)-(CH_2)_nNR_9R_{10}$, $-O-(CH_2)_n$phenyl [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1-C_4alkyl)]$, $-O-(CH_2)_n$pyridine, $-O(CH_2)_nC(O)-(CH_2)_n$pyridine, $-O-(CH_2)_nC(O)O-(CH_2)_n$pyridine, $-O(CH_2)_nC(O)-N(R_9)(CH_2)_n$pyridine, $-O-(CH_2)_n$quinoxalinyl, $-O-(CH_2)_n$quinolinyl, $-O-(CH_2)$npyrazinyl, $-O-(CH_2)_n$naphthyl, $-O-(CH_2)_nC(O)-(CH_2)_n$naphthyl, $-O-(CH_2)_nC(O)O-(CH_2)_n$naphthyl, $-O-(CH_2)_nC(O)NR_9-(CH_2)_n$naphthyl, halo (fluoro, chloro, bromo, iodo), OH, $-(CH_2)_q-OH$, $-(CH_2)_qOC(O)R_9$, $-(CH_2)_qOC-(O)-NR_9R_{10}$, -(1-cyclohexyl-1H-tetrazol-5-yl)C_1-C_4 alkoxy, -[1-

(C_1-C_5alkyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, -[1-(phenyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy [wherein phenyl is optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or -CO_2(C_1-C_4alkyl)], -[1-(pyridinyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, -[1-(1-phenylethyl)-1H-tetrazol-5-yl]C_1-C_4 alkoxy, -C_1-C_4 alkoxyl, or a group of Formula II



wherein R′ is methyl or carboxy, R′′ is hydrogen and R′′′ is selected from benzyl [optionally substituted with one, two or three groups selected from hydroxy, halogen or phenoxy (optionally substituted with one, two or three groups selected from hydroxy or halogen)], C_1-C_5 alkyl, -$(CH_2)_nCO_2H$, -CH_2SH, -CH_2SCH_3, imidazolinylmethylene, indolinylmethylene, $CH_3CH(OH)$, CH_2OH, $H_2N(CH_2)_4$-(optionally in protected form) or $H_2NC(NH)NH(CH_2)_3$ (optionally in protected form); with the overall proviso that at least one member of R_5, R_6, R_7 or R_8 is -CH=CH_2, -O-$(CH_2)_pOH$, -O-$(CH_2)_p$-O-$(CH_2)_n$pyridin-2-yl, -O-$(CH_2)_p$-O-$(CH_2)_n$pyridin-3-yl, -O-$(CH_2)_p$-O-$(CH_2)_n$pyridin-4-yl, -O-$(CH_2)_p$-O-$(CH_2)_n$-1-(C_1-C_4alkyl)-1H-5-tetrazole, -O-$(CH_2)_p$-O-$(CH_2)_n$-pyrimidine, -O-$(CH_2)_p$-O-$(CH_2)_n$-2-benzoxazole, -O-$(CH_2)_p$-O-$(CH_2)_n$-2-benzothiazole, -O-$(CH_2)_p$-O-$(CH_2)_n$-(C_1-C_4alkyl)-triazole, -O-$(CH_2)_p$-O-$(CH_2)_n$-(C_1-C_4alkyl)-imidazole, -O-$(CH_2)_p$-O-$(CH_2)_p$-OR_{15}, -O-$(CH_2)_p$-S-R_{15}, -O-$(CH_2)_p$-O-$(CH_2)_pNR_9R_{10}$, -O-$(CH_2)_p$-S-$(CH_2)_pNR_9R_{10}$, -O-$(CH_2)_p$-S-$(CH_2)_p$-OR_{15}, -O-$(CH_2)_p$-S(O)-R_{15}, -O-$(CH_2)_p$-$S(O_2)$-R_{15}, -O-$(CH_2)_p$-S(O)-$(CH_2)_pNR_9R_{10}$, -O-$(CH_2)_p$-S(O)-$(CH_2)_p$-OR_{15}, -O-$(CH_2)_p$-$S(O_2)$-$(CH_2)_pNR_9R_{10}$, -O-$(CH_2)_p$-$S(O_2)$-$(CH_2)_p$-OR_{15}, -O-$(CH_2)_p$-[4-[$(CH_2)_pOR_{15}$]-1-piperazine], -O-$(CH_2)_p$-[4-(CH)(phenyl)$_2$-1-piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or -CO_2(C_1-C_4alkyl)], -O-$(CH_2)_p$-[4-$(CH_2)_q$phenyl-1-

piperazine] [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-O-(CH_2)_p-$[4-$(CH_2)_q$pyridinyl-1-piperazine] [pyridinyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl, NR_9R_{10} or $-CO_2(C_1$-C_4alkyl)], $O-(CH_2)_p-$[4-(NR_9R_{10} substituted pyridinyl)-1-piperazine, $-O-(CH_2)_p-$(OH substituted 1-piperidine), $-O-(CH_2)_p-$1-pyrrolidin-2-one;

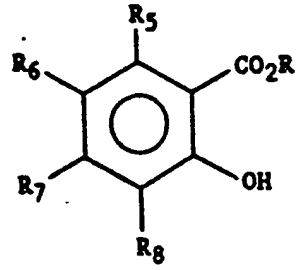
R_{15} is selected from C_1-C_5 alkyl, $-(CH_2)_n$phenyl [phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, OH, trifluoromethyl or $-CO_2(C_1$-C_4alkyl)], $-(CH_2)_n$pyridin-1-yl, $-(CH_2)_n$pyridin-2-yl, $-(CH_2)_n$pyridin-3-yl, $-(CH_2)_n$pyridin-4-yl, $-(CH_2)_n-1-(C_1$-C_4alkyl)-1H-5-tetrazole, $-(CH_2)_n$-pyrimidine, $-(CH_2)_n-2$-benzoxazole, $-(CH_2)_n-2$-benzothiazole, $-(CH_2)_n-(C_1$-C_4alkyl)-triazole, $-(CH_2)_n-(C_1$-C_4alkyl)-imidazole;

n is 0-5;

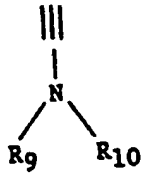
p is 2-5;

q is 1-5;

which comprises reacting a salicylic acid ester of Formula A



with an ynamine of Formula B



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